Book No. 2

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Effect of Chronic Alcohol Feeding on Adrenergic and Cholinergic Neurotransmission Mechanism — CARLOS M. BARATTI, MODESTO C. RUBIO, CARLOS J. PEREC and OSWALDO M. TISCORNIA 21

Membranous Obstruction of the Inferior Vena Cava and Hepatic Veins — PILAR ESPANA, DIEGO FIGUERA, JOSE-MARIA FERNANDEZ DE MIGUEL, ALBERTO ANAYA, JOSEFA MENENDEZ and ALBERTO DURANTEZ 28

Serum Gastrin in Chronic Pancreatitis — L. GULLO, P. VEZZADINI, M. VENTRUCCI, G. BONORA, P. L. COSTA and G. L. FERRI 33

Clinical Vignettes:

- Disseminated Cytomegalovirus Infection with Gastrointestinal Involvement — JANE S. SPIEGEL and ARTHUR D. SCHWABE 37
- Choriocarcinoma of the Stomach — FRED R. SMITH, JAMIE S. BARKIN and GEORGE HENSLEY 45
- Periportal Hepatic Necrosis in Reye's Syndrome — MICHAEL S. BENTZ and CYNTHIA COHEN 49
- Idiopathic Intrahepatic Cholestasis of Pregnancy — PREM S. MISRA, FRANK A. EVANOV, ZELMA WESSELY, GILBERT A. ROSENBLUM and PRITAM SINGH 54
- Syphilitic Hepatitis — NICHOLAS TILIAKOS, JOHN M. SHAMMA'A and SALAH M. NASRALLAH 60
- Inflammatory Fibroid Polyp of the Duodenum — DAVID J. OTT, WALLACE C. WU, DOUGLAS W. SHIFLETT and TIMOTHY C. PENNELL 62
- Intestinal Strongyloidiasis — THOMAS A. BRASITUS, RICHARD P. GOLD, RICHARD H. KAY, ARTHUR M. MAGUN and WILLIAM M. LEE 65

The State of the Art:

- Flexible Sigmoidoscopy—Why, Where and When? — JOHN P. CHRISTIE 70

The Endoscopy Corner:

- Colonic Varices — C. ANDREW PICKENS and FRANCIS J. TEDESCO 73

The Pediatric Corner:

- Peptic Ulcer in Children — KENNETH SCOTT NORD and EMANUEL LEBENTHAL 75

The Radiology Corner:

- Adenomyomatosis of the Gallbladder — HECTOR J. HIDALGO and ANN M. LEWICKI 81

Editorial:

- Our New Look — ARTHUR E. LINDNER 85

News Notes 86

In Memoriam 87

The Last Page — CHARLES G. HAZZI 88

5

45th Annual Convention–Toronto, Canada
12, 13, 14, 15 October 1980

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The stress-secretion relationship in duodenal ulcer*

The best available evidence suggests that anxiety and emotional tension stimulate acid-pepsin secretion.[1] Also, the development of an ulcer crater in predisposed individuals, or the aggravation of ulcer symptoms, is often typically preceded by a stressful event or situation. *Anxiety* in particular seems to play a determining role in the course and prognosis of the disease, as well as its etiology.

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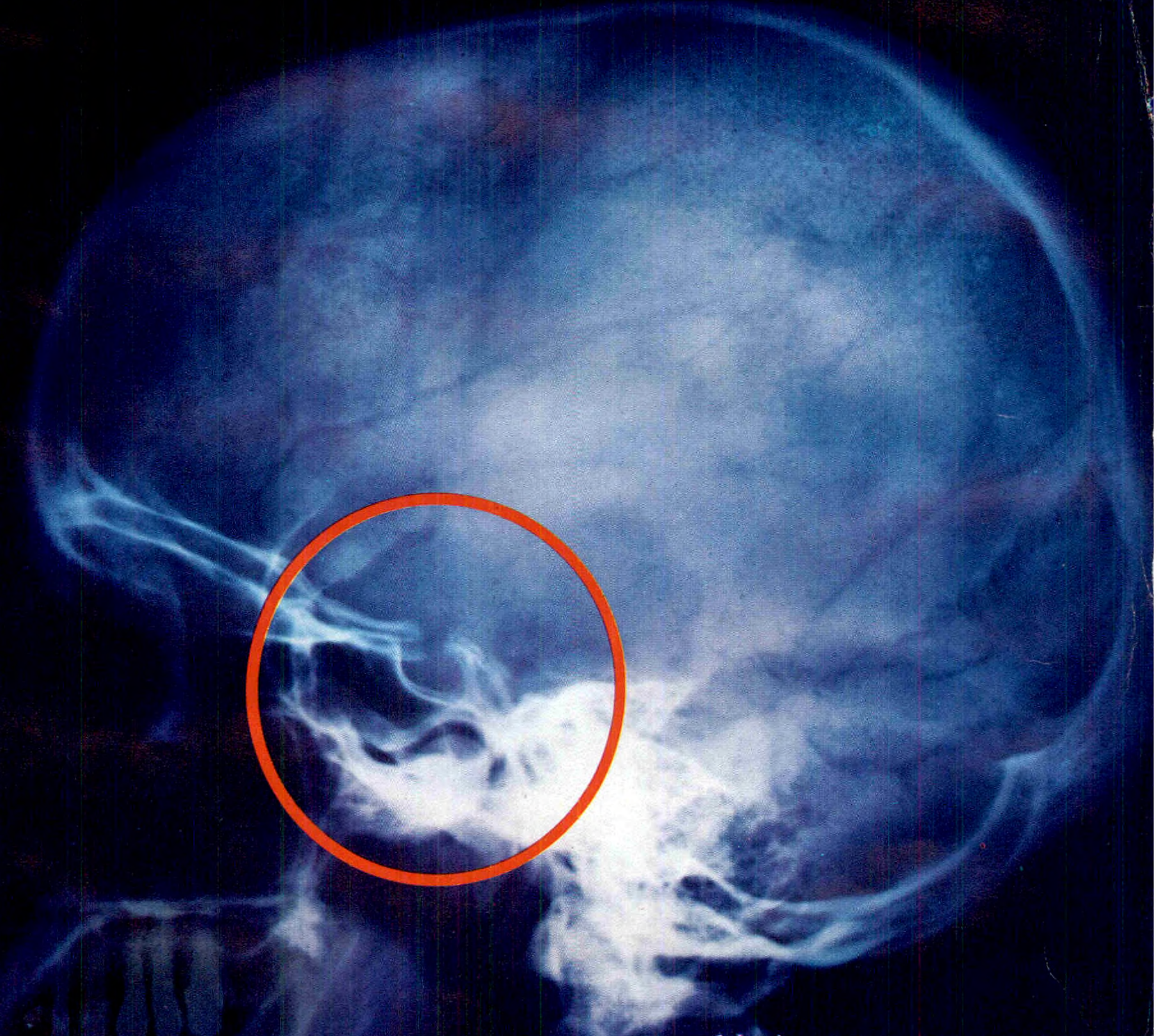

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1. Isenberg J, Richardson CT, Fordtran JS: Pathogenesis of peptic ulcer, chap. 46, in *Gastrointestinal Disease*, ed. 2, edited by Sleisenger MH, Fordtran JS. Philadelphi W.B. Saunders Company, 1978, vol. 1, pp. 800, 801.
2. Sun DCH: Etiology and pathology of pep ulcer, chap. 27, in *Gastroenterology*, ed. 3 edited by Bockus HL, *et al*. Philadelphia W.B. Saunders Company, 1974, pp. 579-

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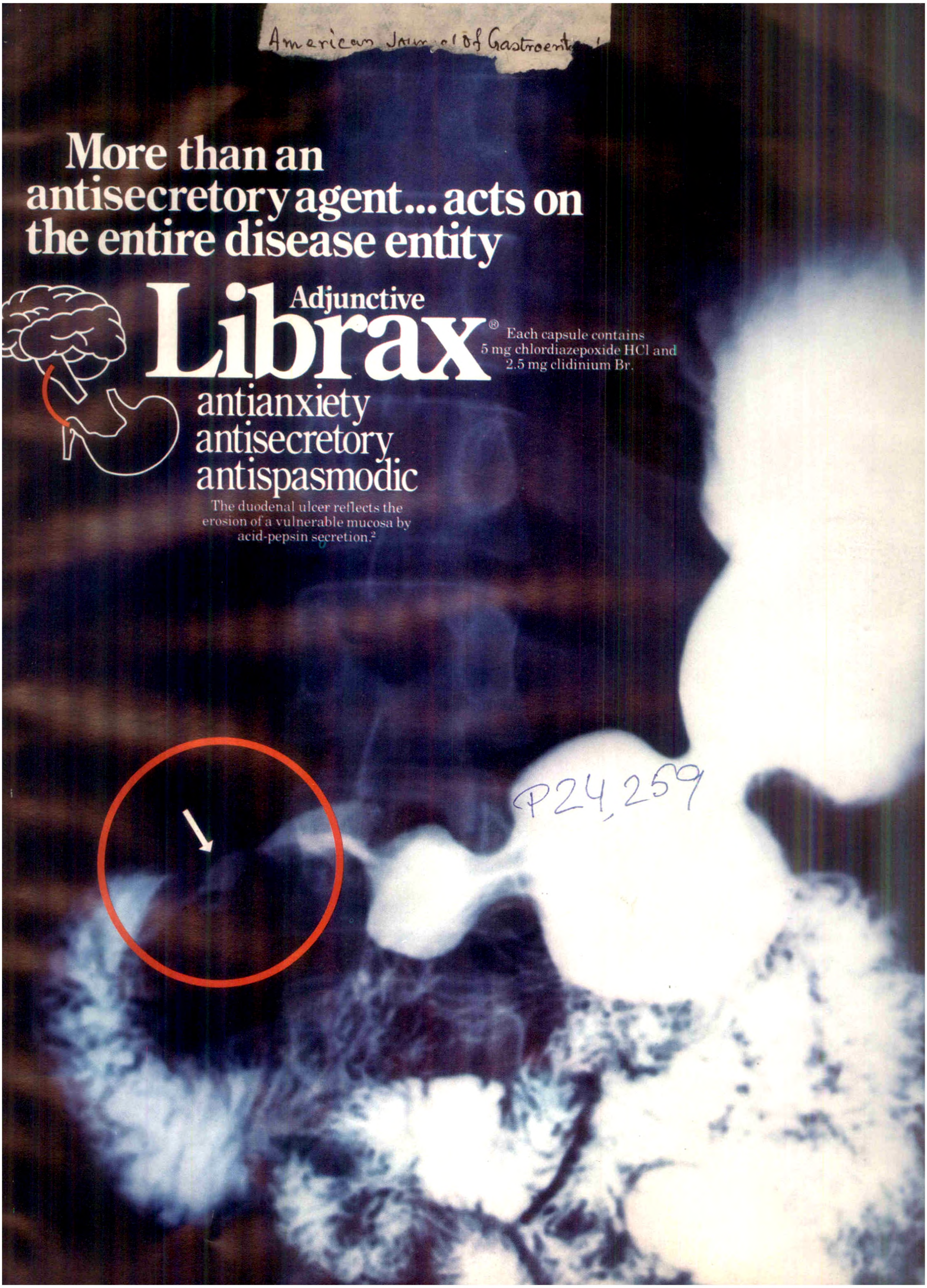

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antianxiety
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The duodenal ulcer reflects the erosion of a vulnerable mucosa by acid-pepsin secretion.[2]

P24,259

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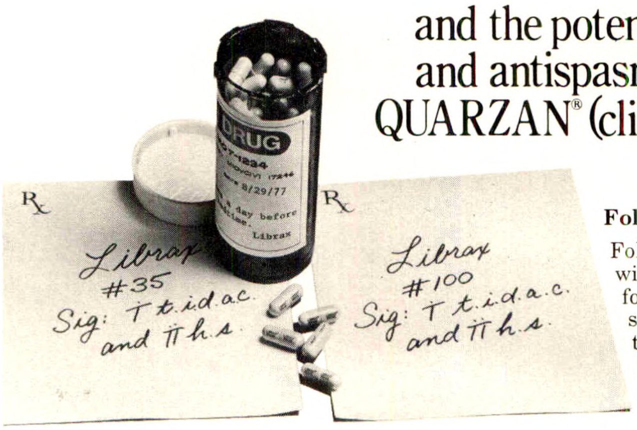

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"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl/Roche) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

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As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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Vol. 73, No. 1 JANUARY, 1980

THE American Journal OF Gastroenterology

(Formerly The Review of Gastroenterology)

The Pioneer Journal of Clinical Gastroenterology, Proctology and Allied Subjects in the United States and Canada

contents:

Editorial Board 4
Instructions to Authors 6
Effect of Chronic Alcohol Feeding on Adrenergic and Cholinergic Neurotransmission Mechanism — Carlos M. Baratti, Modesto C. Rubio, Carlos J. Perec and Oswaldo M. Tiscornia 21
Membranous Obstruction of the Inferior Vena Cava and Hepatic Veins — Pilar Espana, Diego Figuera, Jose-Maria Fernandez de Miguel, Alberto Anaya, Josefa Menendez and Alberto Durantez 28
Serum Gastrin in Chronic Pancreatitis — L. Gullo, P. Vezzadini, M. Ventrucci, G. Bonora, P. L. Costa and G. L. Ferri 33
Clinical Vignettes:
Disseminated Cytomegalovirus Infection with Gastrointestinal Involvement — Jane S. Spiegel and Arthur D. Schwabe 37
Choriocarcinoma of the Stomach — Fred R. Smith, Jamie S. Barkin and George Hensley 45
Periportal Hepatic Necrosis in Reye's Syndrome — Michael S. Bentz and Cynthia Cohen 49
Idiopathic Intrahepatic Cholestasis of Pregnancy — Prem S. Misra, Frank A. Evanov, Zelma Wessely, Gilbert A. Rosenblum and Pritam Singh 54
Syphilitic Hepatitis — Nicholas Tiliakos, John M. Shamma'a and Salah M. Nasrallah 60
Inflammatory Fibroid Polyp of the Duodenum — David J. Ott, Wallace C. Wu, Douglas W. Shiflett and Timothy C. Pennell 62
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The State of the Art:
Flexible Sigmoidoscopy—Why, Where and When? — John P. Christie 70
The Endoscopy Corner:
Colonic Varices — C. Andrew Pickens and Francis J. Tedesco 73
The Pediatric Corner:
Peptic Ulcer in Children — Kenneth Scott Nord and Emanuel Lebenthal 75
The Radiology Corner:
Adenomyomatosis of the Gallbladder — Hector J. Hidalgo and Ann M. Lewicki 81
Editorial:
Our New Look — Arthur E. Lindner 85
News Notes 86
In Memoriam 87
The Last Page — Charles G. Hazzi 88

Index to Advertisers

Colonoscopy Congress 96
McGaw Laboratories .....4th cover
Olympus Corporation of America 12, 13
Ortho Pharmaceutical Corporation 14, 15, 16
Pharmacia Laboratories 94, 95
Roche Laboratories .....2nd cover, 1, 2
Rorer, William H., Co. 17, 18, 19, 20
Rowell Laboratories 92, 93
Smith Kline & French 7, 8, 9, 10
Stuart Pharmaceutical
Div. of ICI Americas, Inc. 5
Viobin Corporation .....3rd cover

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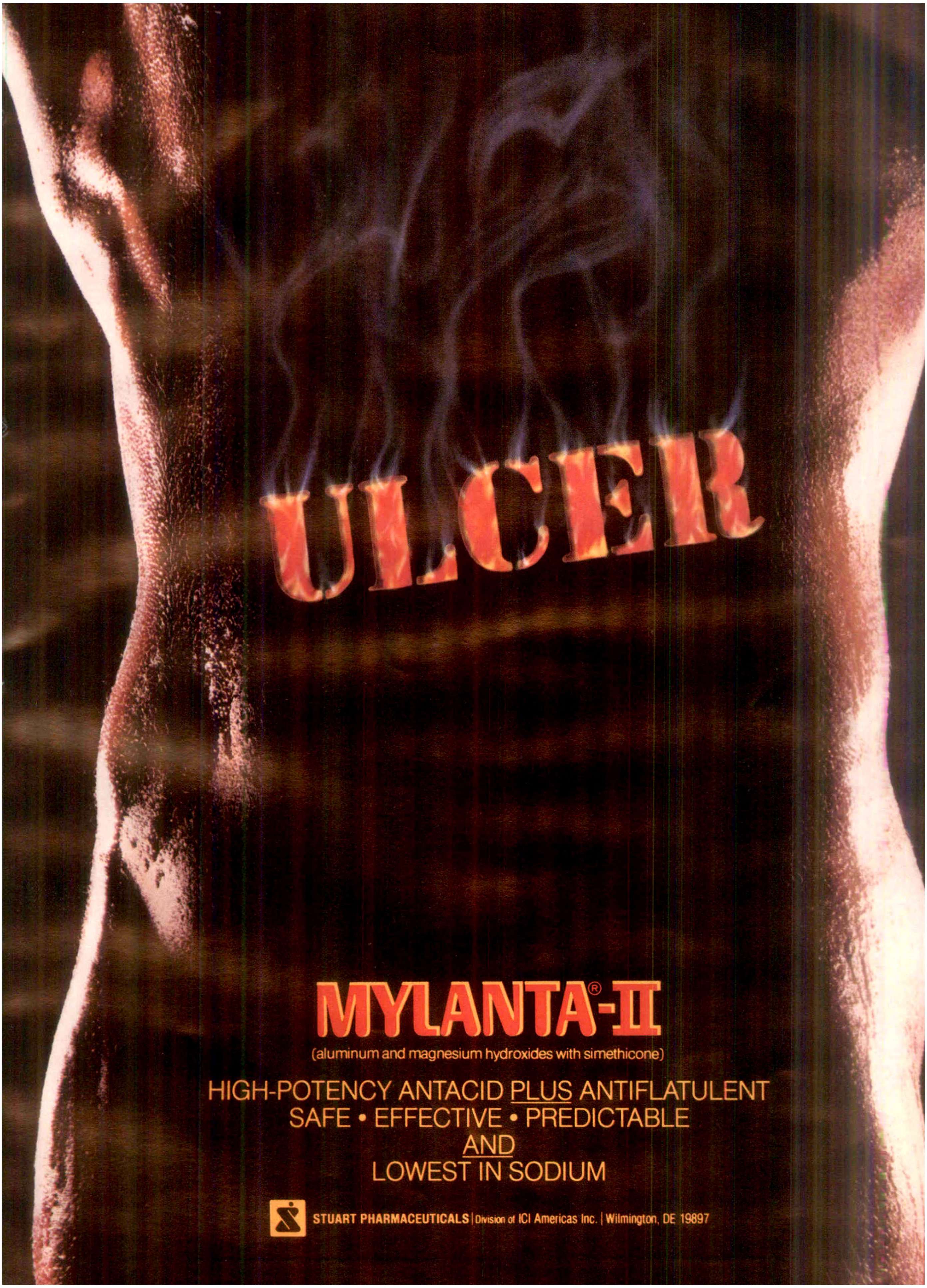

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1. Robinson AS, Sommer DA, Levinson M: Transfiberscopic removal of esophageal polyps. Am J Gastroenterol 61:297-300, 1974.

References to an article with *more than 3 authors:*

2. Starzl TE, Lee IY, Porter KA, et al: The influence of portal blood upon lipid metabolism in normal and diabetic dogs and baboons. Surg Gynecol Obstet 140:381-388, 1975.

Reference to a book:

3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

Reference to an article in a book:

4. Ansel HJ: Normal Pancreatic Duct. In: Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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POSTMARKET
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TA-102

SK&F LAB CO.

'Tagamet'-Two Years Later:

Surveillance Program Confirms Performance and Safety Profile

Please see last page of this ad for brief summary of prescribing information.

Tagamet®
brand of
cimetidine Tablets, 300 mg.
Injection, 300 mg./2 ml.

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'Tagamet' – Two Years Later:

Data Collected from Nearly 10,000 'Tagamet' Outpatients

As part of an ongoing monitoring program of 'Tagamet' performance, more than 1,000 physicians from all over the United States were asked to submit case reports on at least 10 outpatients treated with 'Tagamet'. Information collected included patient history, diagnosis, results of therapy, and any adverse effects. These report forms were evaluated and tabulated to provide incidence of adverse effects in a large, documented patient population. The nature and incidence of adverse effects reported did not differ significantly from those seen in the premarketing clinical studies, as can be seen in the following:

Incidence of Most Frequently Reported Adverse Effects in 9,907 Patients*

Diarrhea	1.0%
Nausea/Vomiting	0.8%
Dizziness	0.3%
Rash	0.3%
Headache	0.2%
Gynecomastia	0.2%
Constipation	0.2%

A few cases of reversible confusional states have been reported, usually in elderly or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. See brief summary of prescribing information on last page of this ad.

*Data on file, SK&F Medical Department.

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Good to Excellent Symptom Relief in Most Duodenal Ulcer Patients Surveyed*

Each physician was asked to evaluate the safety and symptomatic relief of 'Tagamet' therapy in each patient for whom a case report was submitted. No controls were included in this survey, and no attempt to confirm healing was required. The physicians' evaluation of symptomatic relief was as follows:

Results of 'Tagamet' Therapy in Duodenal Ulcer Patients

Excellent (symptom-free)	66%
Good (symptoms substantially relieved)	29%
Fair (little symptom relief)	4%
Poor (poor or no relief)	1%
	100%

*3,666 patients, data on file, SK&F Medical Department.

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Please see following page for brief summary of prescribing information.

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Tablets 300 mg

'Tagamet'—The most thoroughly studied medication to date, for the treatment of duodenal ulcer and pathological hypersecretory states

—Documented effectiveness in duodenal ulcer healing and symptom relief

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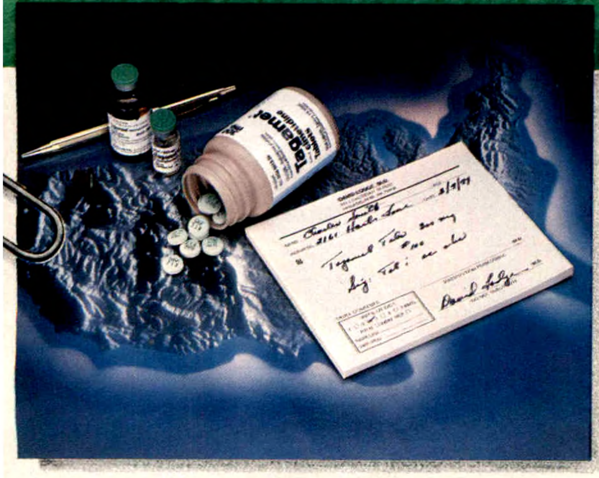

Dosage in Duodenal Ulcer

The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Potentiation of warfarin-type anticoagulants has been observed with concomitant 'Tagamet' administration. For this reason, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when these drugs are administered concomitantly.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials and in 8 ml. multiple-dose vials, in packages of 10.

Date of issuance Mar. 1979

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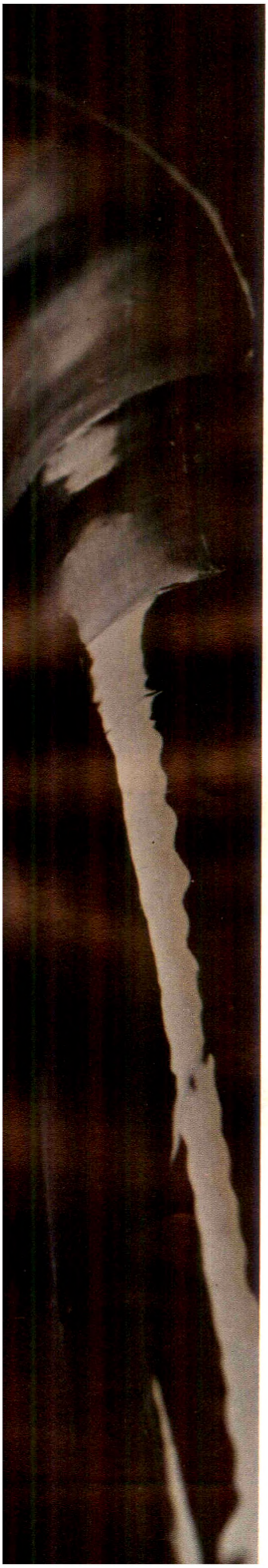

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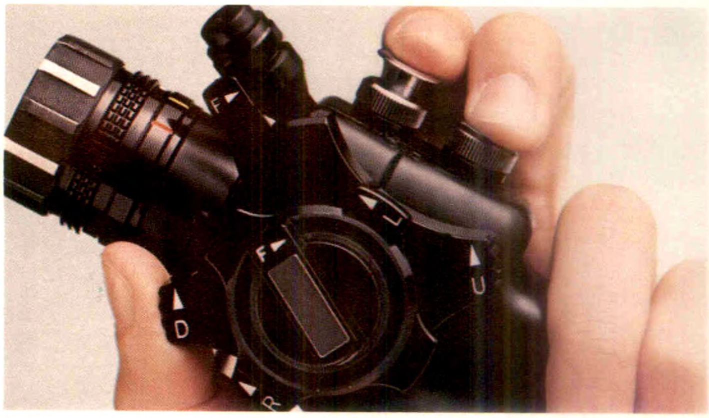

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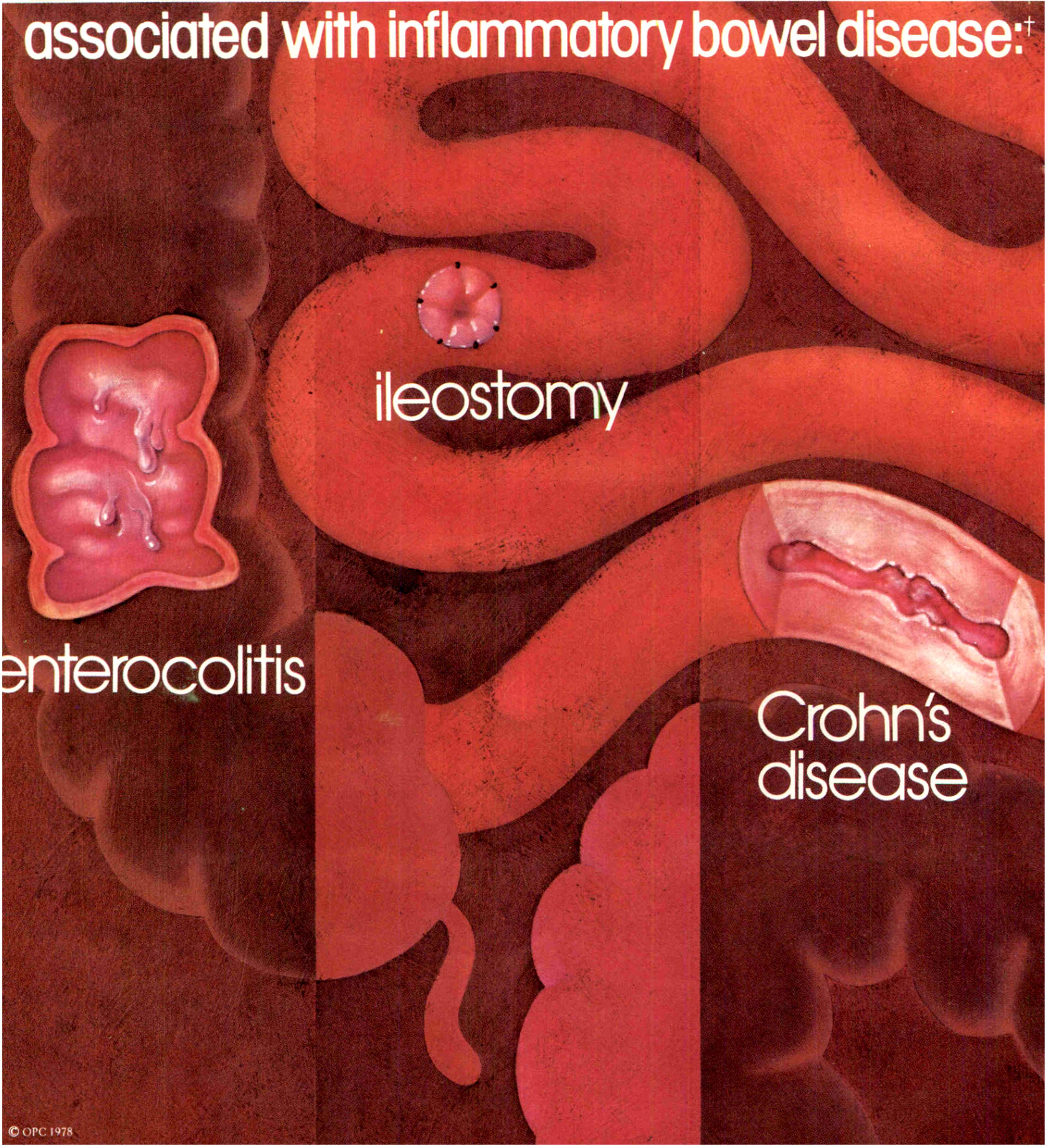
AJG 1

in chronic

DIARRHEA...

associated with inflammatory bowel disease:†



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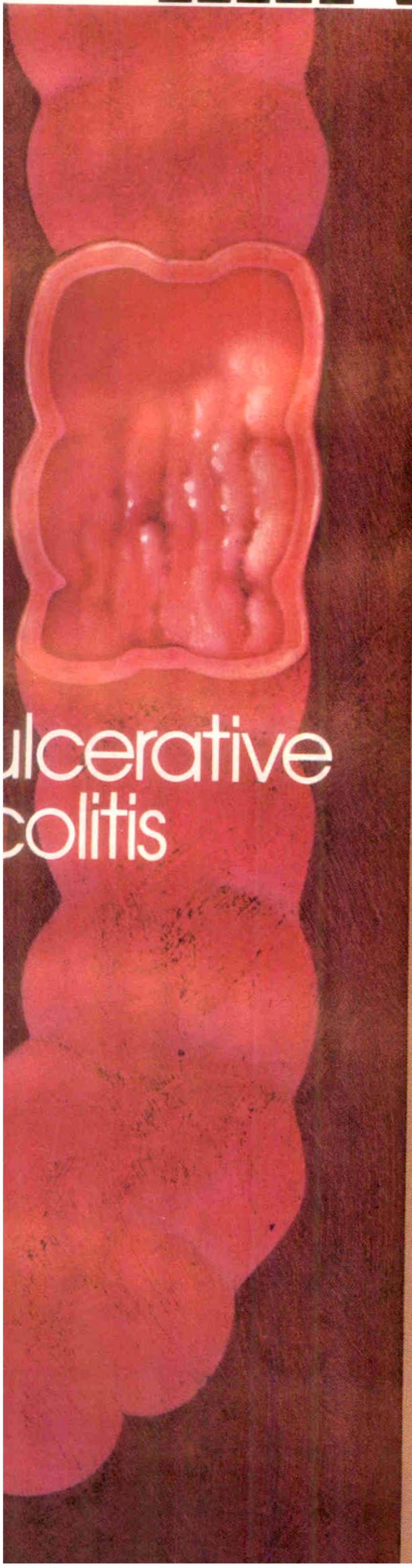
...IMODIUM CV CAPSULES

TRADEMARK

(loperamide HCl)



low incidence of side effects††
IMODIUM is well tolerated—side effects are infrequent, generally of a minor and self-limiting nature, and sometimes difficult to distinguish from the diarrheal syndrome.

compatible with a wide range of medications
In clinical trials exceeding two years, no drug interactions were observed when IMODIUM was used concomitantly with antibiotics, sulfonamides, antihypertensives, barbiturates, corticosteroids and tranquilizers.

no development of tolerance
Tolerance to the antidiarrheal effect of IMODIUM has not been observed to date.

laboratory findings normal in long-term use
No trends toward abnormality were noted in those patients (193 of 358 [54%] with chronic diarrhea) in whom biochemical and hematologic parameters were monitored or in those patients having urinalyses, EKG, and clinical ophthalmologic examinations.

once-daily dosage after titration
The recommended initial dosage is 2 caps *stat*, then 1 capsule after each unformed stool until diarrhea is controlled. Then the daily dosage is reduced to meet individual requirements, and should be given in one single or divided doses.

†Safety and effectiveness in patients under 12 years of age have not been established. Safe use in pregnancy has not been established.

††Please see Prescribing Information on next page.

IMODIUM capsules: an antidiarrheal your patients can stay with

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

Effectively controls diarrhea by normalizing stool frequency and consistency…

Significant improvement in bowel function in 21 patients with chronic diarrhea.

	Median # stools/day	Median stool consistency	Median # caps/day
Relapse period (drug-free)	**8** (Range: 4-30)	**watery**	—
IMODIUM for 1 month	**2** (Range: 1-8) 75% reduction	**soft**	**4** (Range: 2-8)

…yet effectiveness did not diminish in long-term use

Continued effectiveness of IMODIUM in 18 patients after 6 to 18 months[1]

Median number of stools remained constant: **2/day**

Median stool consistency further improved: **soft to normal**

Median daily dosage remained constant: **4 capsules/day**

in chronic diarrhea associated with inflammatory bowel disease:

IMODIUMⒸ Capsules

TRADEMARK

(loperamide HCl)

an antidiarrheal the chronic patient can stay with

"Due to its efficacy, rapid onset and long duration of action, lack of long-term drug tolerance, and simple individualized dosage regimen, [IMODIUM] is likely to become one of the commonly used agents for the treatment of chronic diarrhea."[1]

1. Galambos, J.T. et al.: Gastroenterology 70:1026, June 1976.

Ortho

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

OJ 619R1

Brief Summary: Before prescribing, please consult complete prescribing information, a summary of which follows:

DESCRIPTION: IMODIUM (loperamide hydrochloride), 4-(*p*-chlorophenyl)-4-hydroxy-N, N-dimethyl-α, α-diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use.

IMODIUM Capsules are classified as a Schedule V controlled substance by federal law (see Overdosage Section).

CONTRAINDICATIONS: IMODIUM is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS: Antiperistaltic agents should not be used in acute diarrhea associated with organisms that penetrate the intestinal mucosa, e.g., toxigenic *E. coli, Salmonella, Shigella,* and in pseudomembranous colitis associated with broad- spectrum antibiotics.

Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy. In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. IMODIUM therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop in patients with acute ulcerative colitis.

PRECAUTIONS: In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of IMODIUM should be discontinued.

Abuse and Dependence: Physical dependence to IMODIUM in humans has not been observed. However, studies in monkeys demonstrated that loperamide hydrochloride at high doses produced symptoms of physical dependence of the morphine type.

Carcinogenesis: In an 18 month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis) there was no evidence of carcinogenesis.

Pregnancy: Safe use of IMODIUM during pregnancy has not been established. Reproduction studies performed in rats and rabbits with dosage levels up to 30 times the human therapeutic dose did not demonstrate evidence of impaired fertility or harm to the offspring due to IMODIUM. Higher doses impaired maternal and neonate survival, but no dose level up to 30 times the human dose demonstrated teratogenicity. Such experience cannot exclude the possibility of damage to the fetus. IMODIUM should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether IMODIUM is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children have not been established. Therefore, use of IMODIUM is not recommended in the pediatric age group (under the age of 12). In case of accidental ingestion of IMODIUM by children, see Overdosage Section for suggested treatment.

ADVERSE REACTIONS: The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The following patient complaints have been reported: Abdominal pain, distention or discomfort; constipation; drowsiness or dizziness; dry mouth; nausea and vomiting; tiredness.

Hypersensitivity reactions (including skin rash), however, have been reported with IMODIUM use.

IMODIUM Capsule shells contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.

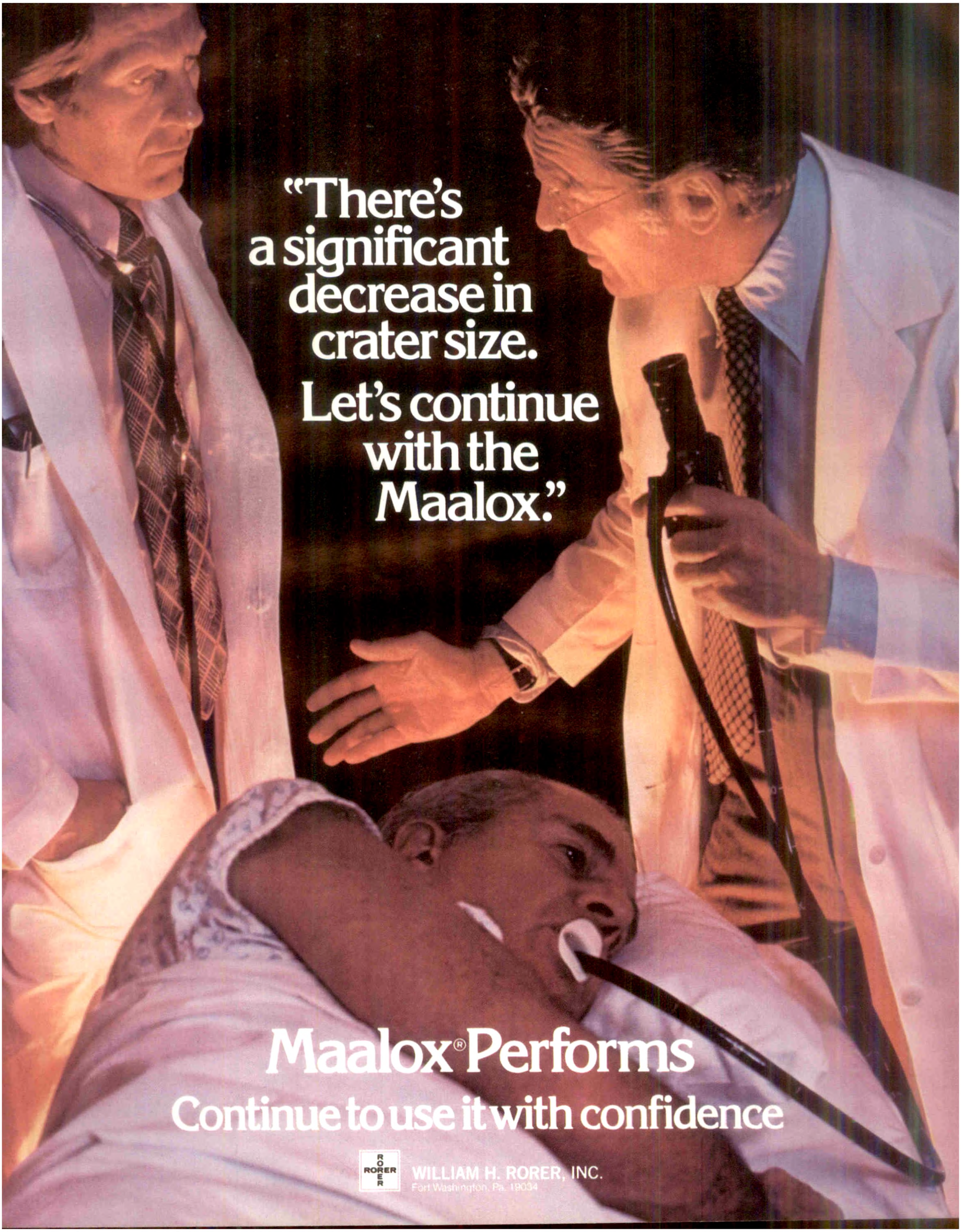
OVERDOSAGE: Animal pharmacological and toxicological data indicate that overdosage in man may result in constipation, CNS depression, and gastrointestinal irritation. In clinical trials an adult who took three 20 mg doses within a 24-hour period was nauseated after the second dose and vomited after the third dose. If vomiting has occurred spontaneously, a slurry of 100 gm of activated charcoal should be administered orally as soon as fluids can be retained.

If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 gm of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone.

In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Based on the fact that relatively little drug is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

HOW SUPPLIED: IMODIUM is available as 2 mg capsules of loperamide hydrochloride. The capsules have a light green body and a dark green cap, with "ORTHO 1000" imprinted on each segment. IMODIUM capsules are supplied in bottles of 100 and 500.

IMODIUM (loperamide hydrochloride) is an original product of Janssen Pharmaceutica, Belgium, and co-developed by Ortho Pharmaceutical Corporation. U.S. Patent 3,714,159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Let's continue with the Maalox."
Maalox® Performs
Continue to use it with confidence
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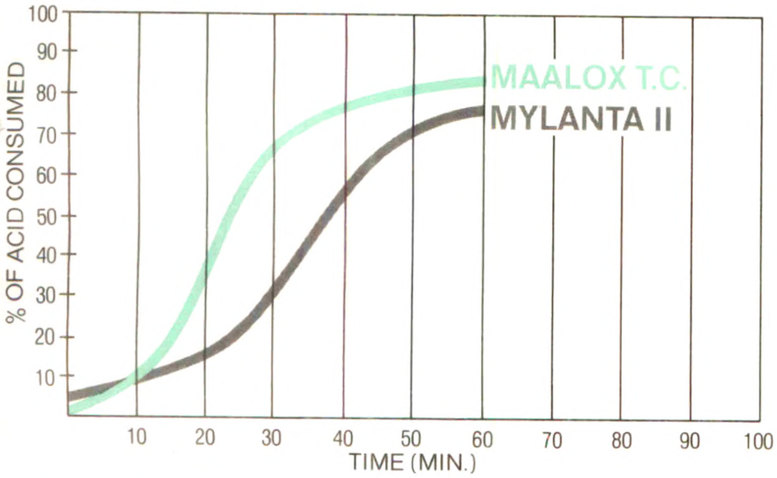

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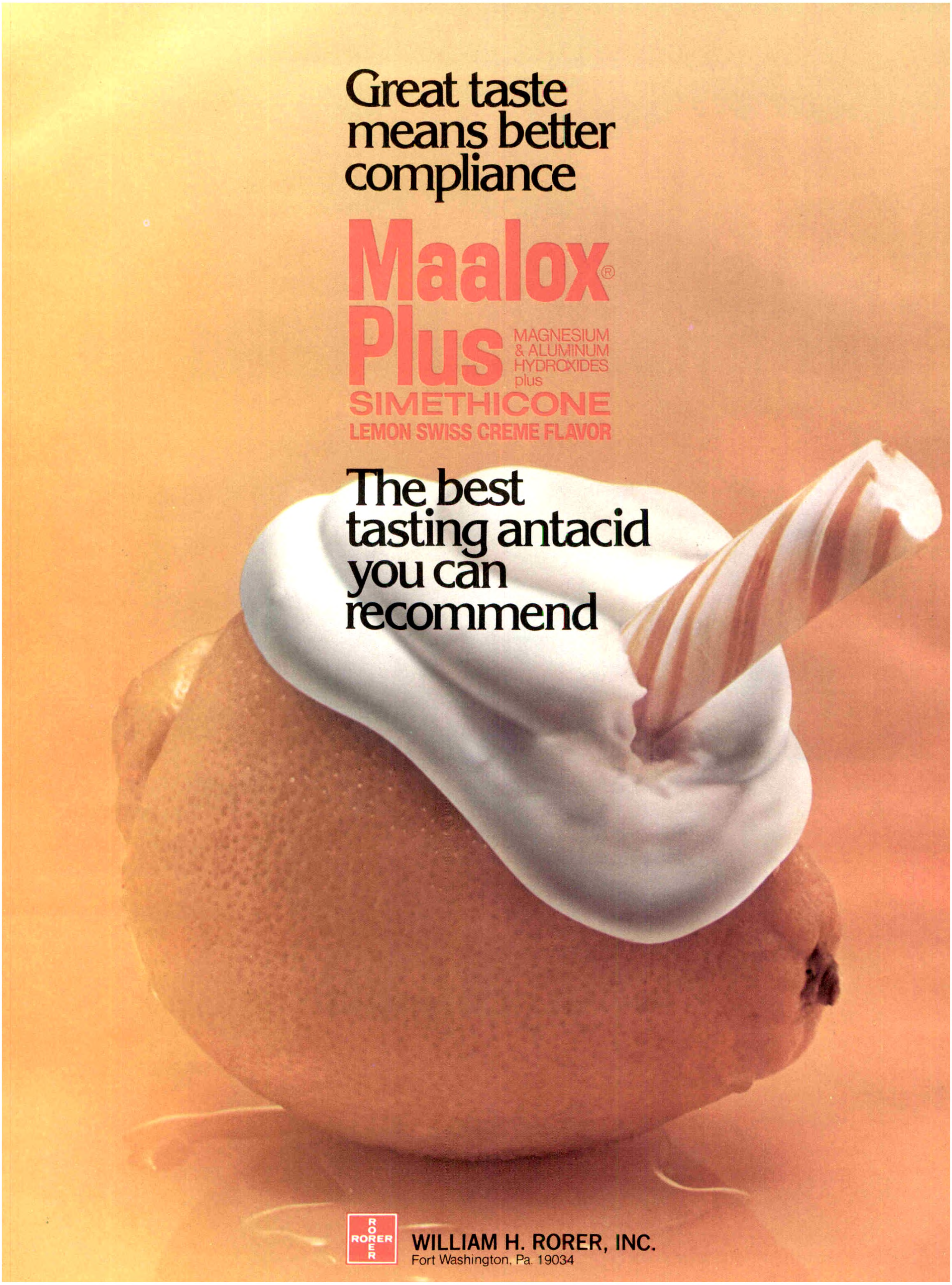

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COMMUNICATION FROM ABROAD

Effect of Chronic Alcohol Feeding on Adrenergic and Cholinergic Neurotransmission Mechanism

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Experimental data is presented indicating that chronic alcohol consumption in rats has a direct CNS effect resulting in increased activity of the autonomic nervous outflow. Changes in neurohormonal transmitters have been demonstrated in four organs: salivary glands, spleen, adrenals and heart. These changes may account for the alterations in end organ sensitivity and secretory patterns which occur in alcoholic animals and man. They may, moreover, represent an initial pathogenetic mechanism whereby alcohol induces its various clinical syndromes.

INTRODUCTION

Previous reports have shown that chronic ingestion of ethanol results in marked morphological and functional changes in exocrine glands and in organs innervated by either branch of the autonomic nervous system.[1, 2] For example, in alcohol fed rats, marked atrophy of the submaxillary gland associated with significant increases in parotid and pancreatic weight per body mass has been reported.[2] In their salivary glands, whose secretory function is mainly controlled by both branches of the autonomic nervous system,[3, 4] the activity of choline acetylase (ChAc) was augmented, the concentration of norepinephrine (NE) was markedly increased[2] and secretory dose response curve to cholinomimetic and sympathetic sialagogue agents showed a marked shift to the right indicating decreased sensitivity.[2, 5] The heart in experimental alcoholism shows both hypertrophy of the ventricles and a remarkable increase in the norepinephrine levels.[2, 6, 7] This rise in neurotransmitter concentrations could be due to several mechanisms: 1. an increase in synthesis resulting from either augmented enzymatic activity or due to increased availability of precursors, e.g. tyrosine or choline; 2. decreased hormonal catabolism, via monoamine oxydase (MAO) or acetylcholinesterase (AChE), pathways; 3. a decrease in neurotransmitter release; 4. an increase in the adrenergic neuronal uptake mechanism.

The experiments herein reported were designed to investigate these hypotheses by studying: 1. synthesis of acetylcholine as judged by the choline acetylase activity in the rat's submaxillary and

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From the Cátedra de Farmacología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires; Instituto de Investigaciones Farmacológicas, CONICET, Cátedra de Fisiología, Facultad de Odontología, Universidad de Buenos Aires and Sección Gastroenterología, Hospital de Clínica, Universidad de Buenos Aires.

* Member of the Carrera del Investigador, Consejo Nacional de Investigaciones Científicas y Técnicas.

† Chief, Gastroenterologic Unit, Hospital de Clínicas.

TABLE I

BODY WEIGHT, SUBMAXILLARY GLAND, ADRENAL AND SPLEEN WEIGHT OF RATS TREATED CHRONICALLY WITH ETHANOL

	Body weight (gm.)	Submaxillary gland (mg.)	Adrenal (mg.)	Spleen (mg.)
Control	227.4 ± 5.70 (n = 11)	155.4 ± 8.3 (n = 10)	57.8 ± 5.40 (n = 10)	774.4 ± 111.6 (n = 6)
Ethanol	173.6 ± 6.25* (n = 16)	75.7 ± 6.7* (n = 10)	39.7 ± 2.31* (n = 10)	335.1 ± 25.7* (n = 8)

Values are means ± S.E.M.
n = number of rats.
* $P < 0.001$ when compared with control group.

TABLE II

ACETYL CHOLINESTERASE ACTIVITY IN THE SUBMAXILLARY AND ADRENAL GLANDS OF RATS TREATED CHRONICALLY WITH ETHANOL

Groups	Tissues	Acetyl cholinesterase	
		μmol/gm./hr.	μmol/gland/hr.
Control	Submaxillary	130.6 ± 8.30 (n = 5)	20.4 ± 1.46 (n = 7)
	Adrenal	5.4 ± 0.22 (n = 10)	0.31 ± 0.01 (n = 10)
Ethanol	Submaxillary	145.7 ± 9.80 (n = 6)	23.6 ± 1.30 (n = 6)
	Adrenal	6.0 ± 0.30 (n = 10)	0.35 ± 0.01* (n = 10)

Values are means ± S.E.M. of n experiments.
* $P < 0.02$ when compared with control group.

adrenal glands;[8] 2. synthesis of catecholamines based upon the activity of tyrosine hydroxylase, the rate limiting step of norepinephrine synthesis[9] (in ventricles, spleen and adrenal glands); activity of phenylethanolamine-N-methyl transferase (PNMT) responsible for the biosynthesis of epinephrine in the adrenal glands;[10] 3. MAO activity[11] (in adrenal glands and ventricles) and AChE in submaxillary and adrenal glands. In addition the neuronal uptake mechanism was also studied in ventricles, spleen and submaxillary glands.

MATERIAL AND METHODS

Adult Wistar rats from both sexes were separated into experimental (n = 26) and control (n = 14) groups. The animals of the experimental group, ages two to three months were allowed to drink only a solution of ethyl alcohol according to the following schedule: first week, a 5% solution (v/v); the next two weeks, 10% (v/v); the following week, 15% (v/v); the fifth week the dose was increased to 25% (v/v) until on the 90th day, the animals received a solution of 32% v/v. All animals were fed with a balanced diet (Purina, Buenos Aires, Argentina) supplied ad-libitum.

At the end of the experimental period all rats were sacrificed by a blow on the neck. The submaxillary glands, spleen, ventricles and adrenal glands were removed, carefully cleaned of adjoining tissue, blotted, dried and weighed.

Assay for choline acetylase activity was performed on an acetone dried powder of the organs prepared according to the method described by Nordenfelt.[12] Choline acetylase activity was measured as described by McCaman and Hunt[13] and Perec, et al.[14] The technic of Ellman, et al[15] with acetyltiocholine as substrate was used to assay acetylcholinesterase. Tyrosine hydroxylase activity was determined on a tissue homogenate as described by Waymire, et al.[16] Phenylethanolamine-N-methyl transferase and MAO activity were studied in the same homogenate using the technics of Ciaranello and Axelrod and McCaman, et al, respectively.[17, 18] The effectiveness of the neuronal uptake mechanism was studied by measuring the uptake of 3H-metaraminol (^{3}H-ME). This amine was selected because of its poor extraneuronal uptake and because it is not a substrate for monoamine oxidase.

The endogenous norepinephrine (NE) content of the organs studied was determined using the trihydroxyindole method as described by Laverty and Taylor[19] after separation of the amine by chromatography on alumina columns.[20] Enzymatic activity was expressed as either total activity (μmoles or nmoles of product formed/hr./organ) or as concentration (μmoles or nmoles of product formed/hr./gm. tissue).

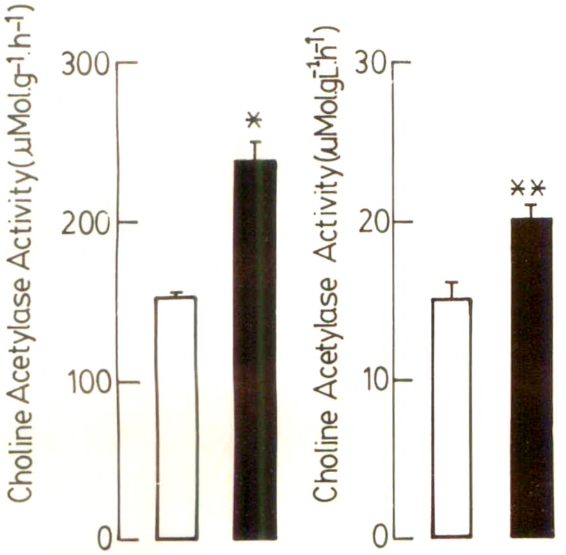

Fig. 1—Choline acetylase activity in the submaxillary gland from normal (□) and ethanol treated rats (■). To the right enzyme activity in µmoles ACh/gl./hr. (total activity) and to the left enzyme activity in µmoles ACh/gm./hr. (concentration).
The values shown are means ± S.E.M. of at least eight experiments.
$^*P < 0.001$; $^{**} P < 0.01$ when compared with control values.

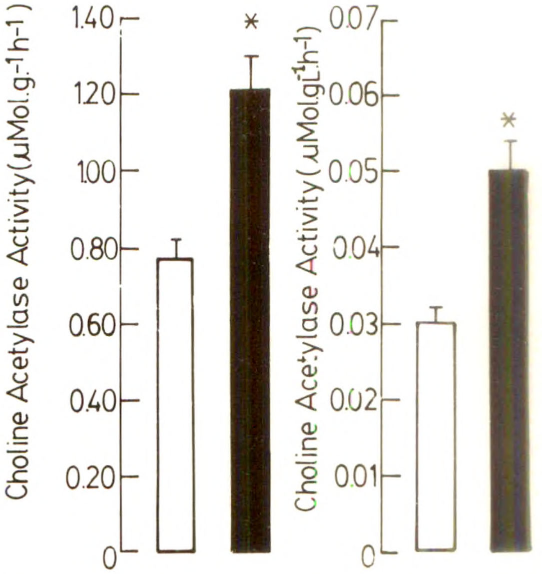

Fig. 2—Choline acetylase activity in the adrenal gland from normal (□) and ethanol treated rats (■). To the right enzyme activity in µmoles/gl./hr. (total activity) and to the left enzyme activity in µmoles/gm./hr. (concentration).
The values shown are means ± S.E.M. of 13 experiments.
$^* P < 0.001$ when compared with control values.

RESULTS

The body weight of rats treated with alcohol was found to be 24% lower than in controls. Table I also shows the ethanol mediated reduction in the weight of the organs studied, i.e. submaxillary glands (about 50%), the adrenal glands (about 31%) and the spleen (57%). The biochemical alterations in neurotransmitter mechanisms can be summarized as follows:

Choline acetylase activity:–Figure 1 shows that the total activity of ChAc in the submaxillary glands of ethanol treated rats was significantly increased by 33% when compared with the enzyme activity found in controls. When calculated as concentration per weight, the glands from treated rats showed an increase of about 50%. This additional increase can be attributed to the decrease in gland weight (see Table I). The adrenal gland revealed an even more striking increase. Total enzyme activity from ethanol treated rats was about two times higher than the values seen in controls, while enzyme activity when calculated as concentration was augmented by 56% (Fig. 2).

Tyrosine hydroxylase and PNMT activities:–Tyrosine hydroxylase (Fig. 3) concentration (nmoles/gm./hr.) and total activity (nmoles/organ/hr.) were significantly increased in ethanol treated rats by 54 and 31% respectively, for the adrenal glands and by 52 and 46% for the ventricles when compared with the values observed in controls. In the spleen, tyrosine hydroxylase total activity was significantly decreased by about 35% but concentration was increased in treated rats about 51%. These differences result from the atrophy of the spleen observed in alcohol fed rats (Table I).

The PNMT enzyme which catalyzes the conversion of norepinephrine to epinephrine in the adrenals (Fig. 4) was found to be higher in both concentration (42%) and total activity (21%) in glands from alcohol treated rats than in controls.

Catabolic enzymes:–The activity of the AChE, responsible for the inactivation of the cholinergic neurotransmitter did not change markedly in the submaxillary and adrenal glands (Table II). There were no differences noted in the enzyme concentration in the submaxillary or in the adrenal glands. A slight increase (about 13%) in the total activity, however, was observed in both organs. This difference was statistically significant only for the adrenal (Table II). On the other hand, previous his-

TABLE III

ENDOGENOUS NOREPINEPHRINE AND (±) – [^{3}H] METARAMINOL UPTAKE IN SUBMAXILLARY GLAND, SPLEEN AND VENTRICLES OF RATS TREATED CHRONICALLY WITH ETHANOL

Tissue	Group	Norepinephrine endogenous		Metaraminol uptake	
		ng/organ	μg/gm.	dpm/organ (x 10^3)	dpm/gm. (x 10^4)
Submaxillary gland	Control	154.6 ± 4.3	1.25 ± 0.04	124.4 ± 14.7	101.4 ± 12.7
	Ethanol	188.7 ± 25.2	2.10 ± 0.25*	72.7 ± 4.9***	83.6 ± 5.7
Spleen	Control	247.2 ± 8.0	1.0 ± 0.08	80.0 ± 4.6	31.6 ± 3.4
	Ethanol	223.2 ± 12.6	1.46 ± 0.13*	77.5 ± 2.8	52.8 ± 5.2*
Ventricles	Control	157.5 ± 14.6	0.40 ± 0.022	93.8 ± 9.0	20.8 ± 1.2
	Ethanol	179.5 ± 18.3	0.61 ± 0.0066*	93.7 ± 13.4	33.7 ± 2.7**

Values are means ± S.E.M. of at least four experiments per group.
* $P < 0.05$; ** $P < 0.025$; *** $P < 0.005$.

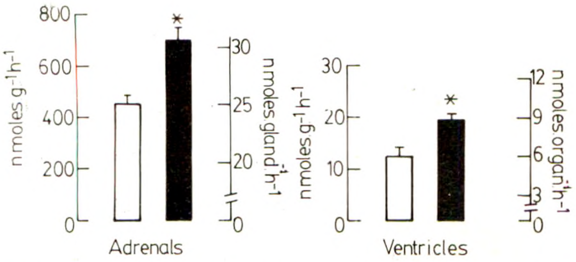

Fig. 3—Tyrosine hydroxylase activity in the adrenal gland and ventricles from normal (□) and ethanol treated rats (■). Right ordinates indicates enzyme activity in nmoles/organ/hr. (total activity) and left ordinates shows enzyme activity in nmoles/gm./hr. (concentration). The values shown are means ± S.E.M. of 13 experiments.
* $P < 0.01$.

tochemical studies indicate that chronic ethanol treatment results in significant depression of AChE activity in the dog's pancreas.[21]

MAO concentration and activity (Fig. 5) was diminished by 50% in alcohol fed rats. Enzyme concentration in the spleen was unaltered by alcohol feeding but total MAO activity was diminished (55%).

Neuronal uptake mechanism:–The uptake mechanism together with biosynthesis regulate the tissues endogenous NE levels.[22, 23] The data in Table III indicate a 46% increase in splenic NE levels in alcohol fed rats. This finding is consistent with previous reports of marked ethanol induced increases in the NE endogenous levels of the submaxillary gland and ventricles.[2, 6]

The effects of chronic ethanolism on the ^{3}H-Metaraminol uptake differed in the tissues studied (Table III). Thus, while the submaxillary showed a significant decrease in the ^{3}H-ME trapped (about 46%), no significant differences were observed in the uptake mechanism in the spleen and ventricles of alcohol fed rats (Table III). These findings suggest that the increase in the endogenous NE levels in the different tissues studied are not related to the changes observed in the neuronal uptake mechanism.

Taken as a whole, the experimental results obtained in chronic ethanol fed rats clearly show an increase in the enzymatic activities inducing biosynthesis of the neurotransmitters of the cholinergic and adrenergic systems as well as increases in the endogenous NE concentration in the organs studied. The following facts should be noted: 1. The different autonomic organs studied showed different quantitative changes in weight. 2. The rise in the activities of the enzymes analyzed varied with the organ studied. 3. Neuronal uptake mechanism was diminished in the submaxillary gland and increased in the two other tissues studied.

In parallel studies to be reported elsewhere, alcohol feeding in rats resulted in increased choline acetylase activity in the brainstem associated with increased ChAc activity of the salivary gland an increase which was not noted when the submaxillary gland was decentralized. Thus, chronic ethanol ingestion appears to exert an effect directly on the parasympathetic and sympathetic autonomic centers of the central nervous system resulting in increased flow of impulses in the peripheral nerves of organs studied.

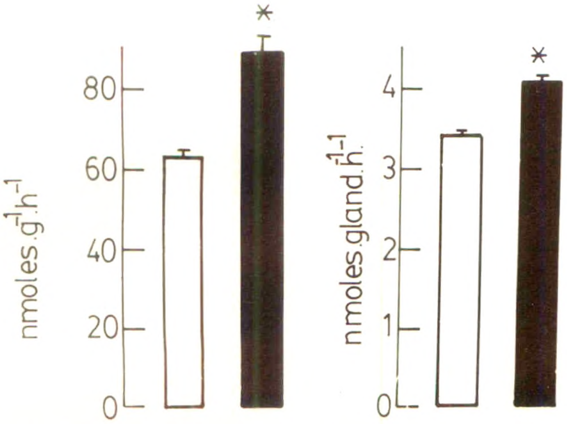

Fig. 4—Phenylethanolamine-N-methyl transferase activity in the adrenal gland from normal (□) and ethanol treated rats (■). To the right enzyme activity in nmoles/gl./hr. (total activity) and to the left enzyme activity in nmoles/gm./hr. (concentration).
The values shown are means ± S.E.M. of 13 experiments.
* $P < 0.005$ when calculated as concentration.
* $P < 0.05$ when expressed as total activity.

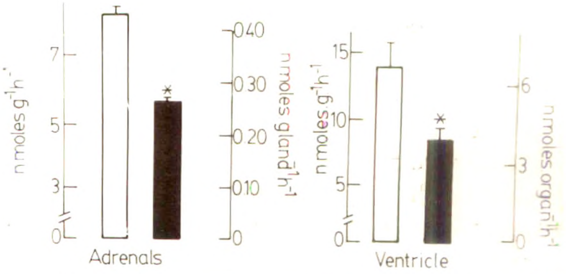

Fig. 5—Monoamine oxidase activity in the adrenal glands and ventricles of normal (□) and ethanol treated rats (■). Right ordinate: enzyme activity in μmoles/organ/hr. (total activity). Left ordinate: enzyme activity in μmoles/gm./hr. (concentration).
The values shown are means ± S.E.M. of 13 experiments.
* $P < 0.025$ when referred to adrenals.
* $P < 0.05$ when referred to ventricles.
Correction:—The ordinates in this Figure should read: μmoles and not nmoles. *Ed.*

Finally the locally effects of alcohol feeding cannot be completely disregarded since differences in sensitivity to exogenous sialogogues have been observed in the denervated salivary glands of the rat fed alcohol as compared with the control.

COMMENT

As indicated in previous results, chronic ethanol feeding resulted in a decrease of body weight of treated rats compared to controls.[2] Chronic ethanol administration induced different effects on organ weight. Some atrophied like the submaxillary and the spleen,[2, 24] others, like the atria and head of the pancreas remain similar to those of their litter mate controls,[2] while the ventricles and the pancreas as a whole undergo hypertrophy.[2, 25]

In the present study, the acetylcholine synthesizing enzyme, choline acetylase which is localized in the cholinergic nerves,[12] has been found to be increased not only in the submaxillary gland[2] but also in the adrenal gland of ethanol fed rats, both when enzyme activity is expressed as a total per organ or when calculated as a concentration. There is also evidence that increased ChAc activity occurs following chronic alcohol administration in the rat and dog pancreas,[2, 21] in the rat's atria and parotid gland[2] but not in the rat ventricles[2] despite extensive parasympathetic innervation on the latter.[26]

The tyrosine hydroxylase data, reflecting the rate of catecholamine biosynthesis indicate augmented production of NE has been induced by chronic ethanol feeding. This conclusion has been suggested by other reports.[24, 27, 28] The increase in activity of adrenal PNMT implies increased adrenal epinephrine in the alcohol fed rats. Since tissue levels of these enzymes are closely correlated with nerve activity,[29–37] these findings suggest that chronic alcohol ingestion increases both cholinergic and adrenergic tone.

The increase in NE probably could not arise from the decreased MAO concentrations since these range about 50%. Pletscher has shown that MAO depletion must reach a level of about 85% in order for the endogenous concentration of biogenic amines to rise.[33] Some local elevation of NE[22, 23] might also be explained by interference with neuronal uptake mechanism. This possibility is suggested by the observed increases in ^{3}H-ME uptake.

SUMMARY

In rats which were alcohol fed for three months, the activity of the enzymes responsible for the synthesis of cholinergic and adrenergic neurotransmitters was studied in submaxillary and adrenal glands, in the spleen and in the heart ventricles. Choline acetylase activity was significantly increased in the submaxillary and the adrenal glands. In the adrenal glands phenylethanol-

amine-N-methyl-transferase was increased while tyrosine hydroxylase activity was significantly augmented in both the adrenal glands and the heart ventricles. These findings provide further evidence that chronic ethanol feeding enhances the cholinergic and/or adrenergic tone in peripheral autonomic innervated organs. These results also suggest that chronic ethanol treatment exerts its effects on the central parasympathetic and sympathetic centers and thereby raises the frequency of impulses in the nerve endings of the organs studied. The increase in the amount of neurotransmitters in contact with the effector cells would be responsible for their decreased responsiveness (subsensitivity) when evaluated with parasympathetic and/or adrenergic agents by means of dose-response curves. These general ethanol-induced influences on the cholinergic and/or adrenergic tone could explain some clinical observations related to changes on the secretory response to hormonal stimulation in patients with chronic alcoholism and pancreatic chronic inflammation.

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COMMUNICATION FROM ABROAD

Membranous Obstruction of the Inferior Vena Cava and Hepatic Veins

BUDD-CHIARI SYNDROME? A TREATABLE DISEASE

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Three cases of membranous obstruction of the inferior vena cava (IVC) are presented. Two of them underwent transcardiac membranotomy with good results. The third patient was treated symptomatically and died from gastrointestinal hemorrhage and hepatic coma two years after the diagnosis of Budd-Chiari syndrome. At autopsy, membranes were found in the inferior vena cava and hepatic veins. Differentiation of Budd-Chiari syndrome secondary to the presence of such a membrane is essential since these patients are potentially curable by surgical treatment. Cavography visualizes the obstruction and is the procedure of choice for diagnosis of this condition. Surgical treatment with transcardiac membranotomy is effective. Some hepatic abnormalities regress after surgery. Prophylactic post-operative treatment with diuretics seems advisable in these patients to prevent congestive cardiac failure.

Malformations of the inferior vena cava (IVC) have been described for many years but were considered of little clinical interest. When IVC ligation or clipping was introduced in surgical practice for the prevention of pulmonary embolisms, undiagnosed IVC malformation, duplication and agenesis of the hepatic portion were observed and their clinical significance in the causation of postoperative complications recognized.

Coarctation of the IVC at its diaphragmatic level was first described by Osler in 1878 but as late as 1950 a case reported in the American literature was considered unique.[1] In 1962, Kimura carried out the first surgical correction of the Budd-Chiari syndrome using transcardiac membranotomy with good results.[2] Thereafter, most of the cases described have been Japanese.

This communication presents three cases of membranous obstruction of the IVC. Two patients underwent transcardiac membranotomy successfully. The other patient did not undergo surgery and died two years after diagnosis. An autopsy was performed showing abnormalities of the IVC and hepatic veins.

CASE REPORTS

Case 1:–A 41-year old male, who presented pedal edema, asthenia, anorexia and dark urine for one year, was first seen in March of 1970. His liver was enlarged to 5 cm. below the costal margin; the spleen was not enlarged and ascites was not pres-

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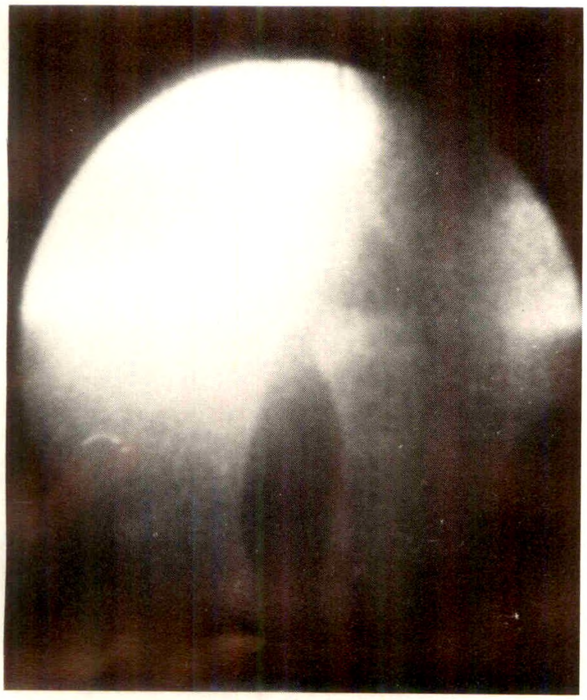

Fig. 1—Case 1. Cavogram. The inferior vena cava is narrowed near the right atrium. No hepatic veins are visualized.

ent. Hemorrhoids and edema of the legs were found. Blood chemistries yielded: Alkaline phosphatase, 40 μK.A.; SGOT, 80 μK.; BSP, 15% at 45 min.; prothrombin time, 60%. No varices in the upper gastrointestinal tract were seen on barium examination. An hepatic biopsy showed zones of fibrous tissue that distorted the hepatic architecture. Proliferation of the internal layer and dilated sinusoids, suggesting Budd-Chiari syndrome, were noted. A cavogram revealed extreme narrowing of the IVC near the right atrium (Fig. 1). From 1970-1972 the patient developed obvious ascites, collateral circulation in the flanks and an enlarged spleen. He suffered several episodes of acute gastric hemorrhage and hepatic coma and died in 1972. At the autopsy, an infundibular stenosis of the IVC, ending in a thin membrane with a 2 mm. central hole, was found 3 cm. from the right atrium (Figs. 2a and 2b). Another membrane covered the ostium of a hepatic vein. Just under the IVC membrane was the ostium of the medial hepatic vein into which flowed three large tributaries at the level of the quadrate lobe: one coming from the inferior half of the right lobe, another from the middle of the left and right lobes and, the last one, a hairpin vessel that received branches from the inferior half of the left lobe and the quadrate lobe (Fig. 3). Microscopic study of the membrane showed fibrous and elastic tissue. Neither smooth nor striated muscle was found. Ostia of the left or right hepatic veins were not seen. Hepatic histology was normal in the well-vascularized areas; in the poorly vascularized areas fibrosis and infarcted zones were found. No thrombus was found either in the IVC or the hepatic veins. Eroded varices were seen in the inferior third of the esophagus. The stomach contained 2,500 cc. of black blood. Blood was also found through the rest of the digestive tract. The spleen weighed 370 gm.

Case 2:–A 36-year old female suffered from thrombophlebitis in her right leg since age 28. She had also developed edema and ulcerated varices three years before and complained of vomiting and recurrent pain in the upper right abdomen. Upon examination, postphlebitic nonulcerated lesions were found in her right leg. Edema to the knees was present bilaterally. The liver was palpable 8 cm. from the costal margin. The spleen was not palpable. There was cephalad collateral circulation in the abdominal wall. Serologic evaluation revealed an alkaline phosphatase of 28 μK.A. and BSP, 31% at 45 min. No varices were seen in the esophagus in the barium examination. Liver biopsy revealed thick connective tissue which did not affect the portal spaces and contained small nodules of hepatic cells. Dilated sinusoids and thickened parietal veins were present. Catherization of the IVC through the right humeral and the right femoral veins was carried out with simultaneous contrast injection. Obstruction of the IVC was found 1 cm. below the right atrium; the right hepatic vein was patent but not the left. The pressure gradient between the IVC below the obstruction and the right atrium was 22 mm. Hg. In July, 1972, she underwent surgery using extracorporeal circulation. The right atrium was opened and a membrane, which obstructed the IVC, was found. The membrane was incised and the caval lumen digitally dilated. After this procedure, the pressure gradient was 1 mm. Hg. During the immediate postoperative period, the patient had oliguria and signs of congestive failure. She was treated with diuretics with rapid reversal of cardiac insufficiency. Two weeks after the operation, another catheterization was performed, showing an unobstructed IVC. One year later, hepatic biopsy showed only isolated residual fibrosis and parietal thickening of the centrolobular

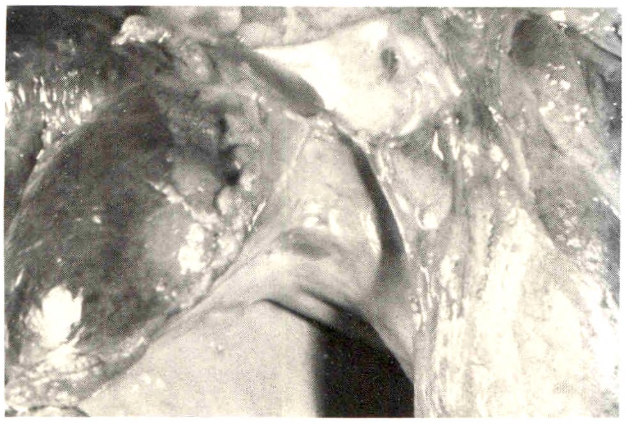

Fig. 2a

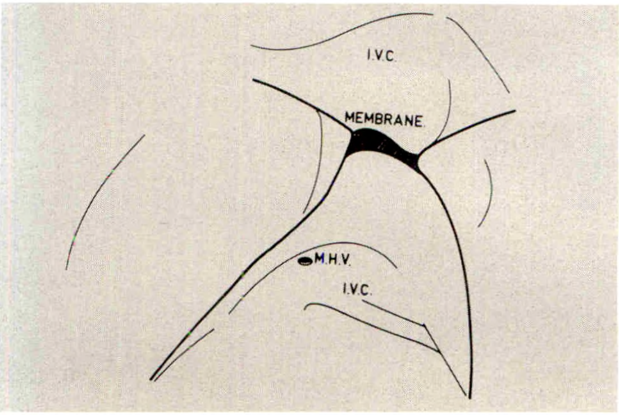

Fig. 2b

Figs. 2a and 2b—Case 1. Posterior view. Infundibular zone and membrane in IVC. The ostium of the medial hepatic vein is visible. Small hepatic vein ostia are observed in the wall of the IVC.

veins. Five years after surgery, she has remained asymptomatic.

Case 3:–A 28-year old male was seen in consultation in November of 1973. In August, he had suffered chest pains, intense headache, vomiting on two occasions and loss of sight in both eyes. On examination, prominent bilateral papilledema was present without other abnormal neurological findings. The liver was felt 4 cm. from the costal margin, the spleen was not palpable. Serological analyses were as follows: alkaline phosphatase, 26 μK.A.; SGOT, 60 μK.; BSP, 20% at 45 min.; prothrombin time, 58%. The EEG was normal. Chemistry and bacteriology of the CFS was normal. A hepatic biopsy showed dilation of sinusoids and centrolubular vein congestion without significant thickening or fibrosis. Coagulation studies were normal. Cavography disclosed membranous obstruction of the IVC near its union with the right hepatic vein; no left hepatic vein was seen. The azygos vein was dilated. The pressure gradient between the IVC below the obstruction and the right atrium was 20 mm. Hg. While the patient was hospitalized, moderate ascites and edema of the ankles developed. In December of 1973, he underwent a transcardiac membranotomy without extracorporeal circulation. The postoperative course was benign. Prophylactically treated with diuretics, he developed neither oliguria nor pulmonary edema. A month later, catheterization showed an unobstructed IVC. The pressure gradient was 8 mm. Hg. A year and a half after surgery, the patient had a slight visual impairment and no new neurological symptoms had appeared.

COMMENT

Membranous obstruction of the IVC with secondary Budd-Chiari syndrome is characterized by signs and symptoms of IVC hypertension and portal hypertension.[3–5] The first symptoms to appear are usually those of hypertension in the IVC, i.e., varices in the legs, collateral circulation in the flanks or anterior abdominal wall, hepatomegaly and ascites. In more advanced states, splenomegaly, esophageal varices, jaundice, abdominal pains, vomiting and gastrointestinal hemorrhage, appear. If surgical decompression is not performed, the symptoms of portal hypertension become more prominent and the patients generally die of gastrointestinal hemorrhage or from hepatic coma. The first clinical symptoms appear in the early 20's, the progression of symptoms is slow, varying from two to 12 years, although cases with 20 years' evolution have been described.[4]

The membrane is considered to be congenital,[3–7] because its histology is similar to that of the wall of the IVC and also because in all cases the membrane obstructs the vena cava at the same level, i.e. at its passage through the diaphragm, generally below the left hepatic vein. At this level, major vascular embryologic changes take place so that diverse anomalies can occur.[6, 8, 9] Kilman, et al,[10] stress the anatomic points of congenital malformation at which venous obstruction of the hepatic veins or the IVC occurs: 1. The hepatocardiac junction with the right atrium. 2. The junction of the hepatic portion of the vena cava with the right hepatocardiac channel. 3. The orifices of the hepa-

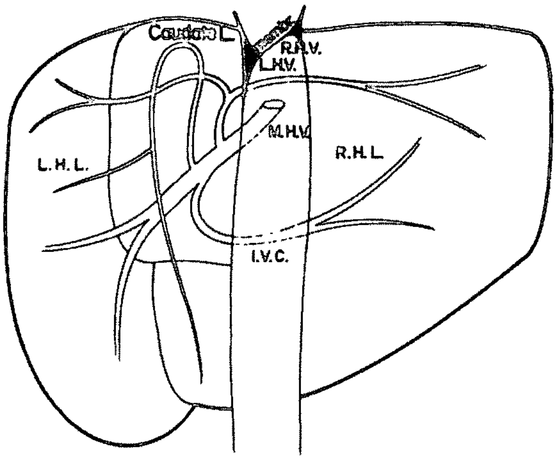

Fig. 3—Venous hepatic circulation in Case 1. The medial hepatic vein (MHV) received blood from all hepatic lobes. Left hepatic lobe (LHL). Right hepatic lobe (RHL). Left hepatic vein (LHV). Right hepatic vein (RHV).

tic veins contributing to the development of the caval system.

The type "a" malformation is called "persistent Eustachian valve" and produces clinical manifestations similar to the Budd-Chiari syndrome;[10] malformations of types "b" and "c" produce membranous obstruction of the IVC at its diaphragmatic level and at the ostia of the hepatic veins, similar to the findings in the patients reported. The membranous malformation affects both the IVC and the hepatic veins in 72% of the cases; in 18%, there is exclusive obstruction of the IVC and in 10%, only the hepatic veins are occluded.[11] Thrombosis of the IVC or the hepatic veins associated with the congenital membrane has been observed in several cases. It is thought to be secondary to obstruction of venous flow caused by the membrane but thrombosis also occurs after surgical correction of the obstruction,[12, 13] especially when anastomoses or grafting of the IVC are necessary.

IVC malformation should be suspected when abdominal collateral circulation or multiple episodes of thrombophlebitis are observed in a young adult. Diagnosis is confirmed by cavogram, which locates the membrane, defines the patency of the hepatic veins and reveals thrombosis. Some authors advise double catheterization, using simultaneous contrast injection through the subclavian and femoral veins.[4, 8] Venous pressure measurement of the legs was reported to be a useful indication of IVC obstruction.[14] Serologic studies, including tests of hepatic function, are not helpful in diagnosis.

Hepatic vein thrombosis, thrombosis of the IVC and the presence of a congenital membrane, including the IVC one, cannot be diagnosed by liver biopsy or by hepatic vein catheterization because the histologic and radiographic changes are not distinctive. Cases of congenital IVC membranes have probably been misdiagnosed because its clinicopathologic presentation can be confused with hepatic vein thrombosis.

At present, it is thought that transcardiac membranotomy is the treatment of choice, except when the thickness of the membrane or associated thrombosis renders this procedure impossible. In such cases, grafts of teflon or pericardium.[6, 15] saphenous vein by-pass, splenoazygous shunt[20] or azygocaval anastomosis,[5] have been recommended.

In the immediate postoperative period, pleural effusion and signs of congestive heart failure are often seen. Drainage of pleural effusion has been suggested as treatment of this cardiac insufficiency which disappeared in a few hours after diuresis. Case 2 was treated prophylactically with diuretics and did not develop heart failure. Cardiac insufficiency in the immediate postoperative stage can be attributed to increased venous return from edema reabsorption. Diuretics, therefore, are indicated during this period.

SUMMARY

Three cases of congenital membrane IVC obstruction are presented to illustrate the symptom complex, its diagnosis and the surgical treatment.

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COMMUNICATION FROM ABROAD

Serum Gastrin in Chronic Pancreatitis

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Fasting serum gastrin and gastrin response to a protein meal were measured in a group of patients with chronic pancreatitis and in controls. No significant differences were found between the two groups of subjects. In patients with chronic pancreatitis no relation was found between gastrin release and the severity of pancreatic exocrine insufficiency.

Gastric acid secretion in patients with chronic pancreatitis has been studied by several investigators.[1-3] On the contrary, very little is known about gastrin in this disease. Experimentally, elevated serum levels of gastrin have been observed in dogs with pancreatic insufficiency secondary to pancreatic duct ligation.[4] Moreover, in dogs treated chronically with ethanol, Treffot, et al[5] found a greater gastrin-releasing capacity than in control animals. This alcohol-induced excess of gastrin has been considered as a possible factor contributing to the hyper-concentration of enzymatic proteins in the pancreatic juice and to the intraductal precipitation of protein plugs in alcohol-induced pancreatitis.[6]

The present paper describes serum gastrin levels in the fasting state and after ingestion of a protein meal in a group of patients with proven chronic pancreatitis and in controls. The aim of the study was to investigate the release of gastrin in patients with chronic pancreatitis.

MATERIAL AND METHODS

Fourteen patients, 13 males and one female, with chronic alcoholic pancreatitis were studied. All of them had a history of excessive intake of alcohol (more than 150 gm. of pure alcohol per day) for many years (more than five years) prior to the onset of the disease. The diagnosis was confirmed by radiological evidence of pancreatic calcification in 11 cases and by histological examination of surgical pancreatic specimens in the remaining three. All had pancreatic exocrine insufficiency as determined by the secretin-cerulein pancreatic test.[7] None had clinical, biochemical or radiological evidence of other disease apart from pancreatitis. Their ages ranged from 26-60 years, with a mean of 42. The interval between the clinical onset of the disease and the study ranged from one to 23 years, mean 7.5.

Eight healthy volunteers, six males and two females, free of gastrointestinal disorders, constituted the control group. Their ages ranged from 20-62 years, with a mean of 43.

The test was performed in the morning, after an overnight fast. Two basal blood samples were taken at − 15 and 0 minutes and then a protein meal (Liebig meat extract, 15 gm. in 150 ml. of water) was administered. Further blood samples were obtained at 15, 30, 60 and 120 minutes after the meal. The serum was immediately frozen until assayed for gastrin. Gastrin was determined by a radioim-

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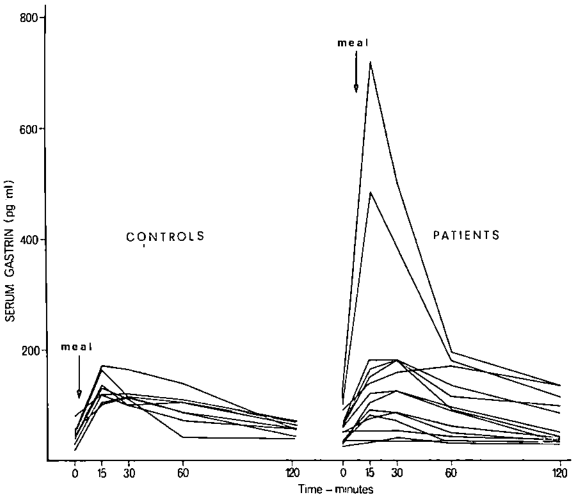

Fig. 1—Individual serum gastrin responses to a protein meal in controls and in patients with chronic pancreatitis.

munoassay method previously described.[8] Antiserum AGR 2 produced in rabbits against synthetic C-terminal hexadecapeptide of human non sulfated gastrin (G 2-17 I) was used. With this antiserum, G 2-17 I, human nonsulfated and sulfated heptadecapeptide gastrin (G 17 I and II) and big gastrin (G 34 I and II) are measured with equimolar potency. G 2-17 I was used as the standard and I^{125}-labeled G 2-17 I as the tracer. Immunoreactive gastrin was expressed as pg. equivalent of G 2-17 I/ml.

The mean value of the two fasting samples was taken as the fasting value. The highest gastrin concentration after the meal was taken as the peak. The integrated gastrin response was calculated by adding the values of gastrin concentration which were greater than the fasting value and subtracting the product of the fasting value and the number of samples taken when gastrin concentration was increased.

The Mann-Whitney U test was utilized for statistical analysis.

Results

Figure 1 shows the individual gastrin responses to the ingestion of a meat meal in control subjects and in patients. In control subjects there was a prompt and significant rise of gastrin levels after the meal. From a fasting value of 45 ± 5.6 pg./ml. (mean ± SEM) gastrin concentration rose to 131 ± 8.8 pg./ml. at 15 minutes and decreased progressively thereafter. The majority of chronic pancreatitis patients had both fasting levels of gastrin and gastrin concentration after the meal in the range of controls. From a mean fasting value of 56.5 ± 7.5 gastrin concentration rose to 173.7 ± 51.5 at 15 minutes after the meal and decreased progressively thereafter. In three patients the ingestion of the meal did not cause any significant increase of gastrin, whereas in two cases the release of gastrin after the meal was very high.

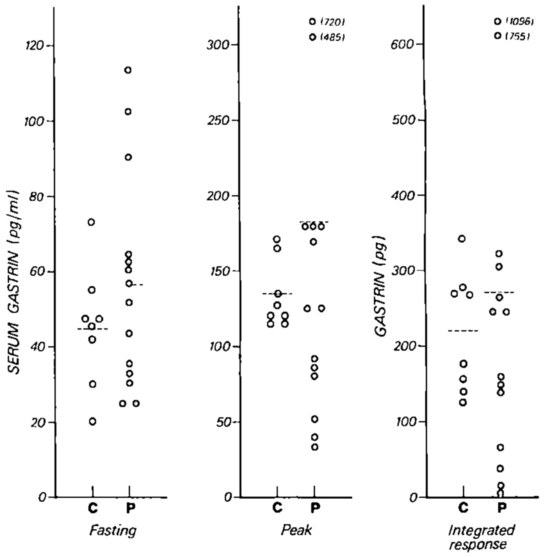

Fig. 2—Individual values of fasting gastrin, peak gastrin after the meal and integrated gastrin responses. Broken horizontal line: mean; C: controls; P: patients.

Figure 2 shows the individual values of fasting gastrin, of peak gastrin after the meal and the integrated gastrin responses. The differences between the two groups of subjects are not statistically significant.

No correlation was found between integrated gastrin responses and lipase output in patients with chronic pancreatitis (Fig. 3).

Comment

The present study has shown that gastrin release is normal in the majority of patients with chronic pancreatitis. As far as we know, the only available data on this subject are those of Kalk, et al[9] who measured plasma gastrin responses to intravenous infusion of arginine in 18 patients with chronic pancreatitis and found normal response in most of them. The results of the present study agree with the observations of Kalk, et al.[9] In fact, the

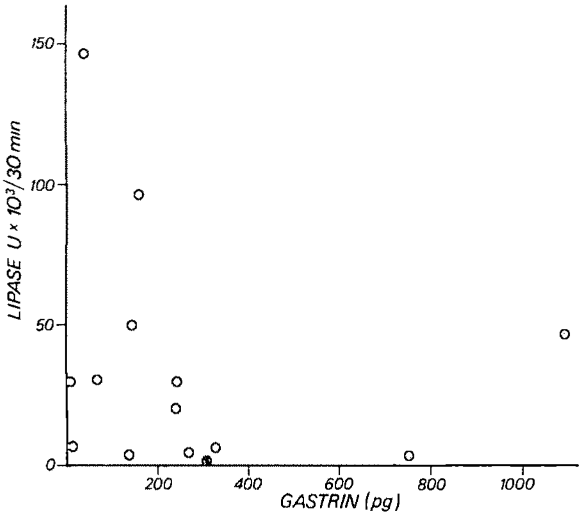

Fig. 3—Relationship between integrated gastrin response and lipase output in patients with chronic pancreatitis.

majority of patients studied showed both fasting values of gastrin and gastrin levels after the meal in the range of control subjects. In three patients there was no gastrin response to the ingestion of the meal. A similar finding was also observed by Kalk, et al[9] after arginine infusion in three of their patients. Absent gastrin response to a protein meal has also been observed in some healthy subjects by McGuigan and Trudeau,[10] indicating that a protein meal may not invariably stimulate gastrin release. The possibility, however, of the existence in the above three patients of antral gastritis induced by alcohol is not to be excluded. In two of the 14 patients studied the release of gastrin after the meal was very high. Fasting concentrations of gastrin were also higher than those in control subjects. These two patients had a normal radiological pattern of the stomach and the duodenum. The study of acid secretion with pentagastrin showed low acid output. We did not carry out a histological study of the gastric mucosa in these two patients, so it is difficult to interpret the mechanism of the increased release of gastrin. Considering, however, that superficial or atrophic gastritis is frequent in heavy alcoholics,[11] the possibility that the hypersecretion of gastrin together with acid hyposecretion is due to the presence of alcoholic gastritis without extensive antral involvement seems quite likely.

In experimental animals complete loss of pancreatic juice causes gastric acid hypersecretion.[12] In patients with chronic pancreatitis, comparisons between gastric acid secretion and exocrine pancreatic function have led to conflicting conclusions.[1–3] It seems, however, from a recent study of Saunders, et al[3] that in patients with severe pancreatic insufficiency gastric acid hypersecretion is common. The mechanism of acid hypersecretion is not completely known. In part, it is the result of defective gastric inhibition from the small intestine.[3] In dogs with pancreatic atrophy following pancreatic duct ligation, Basso, et al[4] found elevated serum gastrin levels. Based on this finding, they suggested a possible role of gastrin in the pathogenesis of increased acid secretion secondary to pancreatic insufficiency. In the present study we did not find any correlation between gastrin release and the severity of pancreatic insufficiency. In particular, we did not observe elevated gastrin levels in patients with more severe pancreatic insufficiency (six patients had lipase output below 10% of normal and steatorrhea). We did not carry out a systematic study of gastric acid secretion in our patients, so we cannot draw a definitive conclusion about the relations between gastrin and gastric secretion of acid in pancreatic insufficiency. The present data, however, seem to indicate that in man, pancreatic exocrine insufficiency, even if severe, is not associated with increased gastrin release. Moreover, the results indicate that the increased gastrin-releasing capacity observed in dogs treated chronically with ethanol does not occur in alcoholic man affected by chronic pancreatitis, at least not in the advanced stage of the disease, when the patients of the present study were investigated.

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CLINICAL VIGNETTE

Disseminated Cytomegalovirus Infection with Gastrointestinal Involvement

THE ROLE OF ALTERED IMMUNITY IN THE ELDERLY

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Disseminated cytomegalovirus (CMV) infections seem to occur in patients with impaired immunity. The evidence for the altered immunity and the predisposing factors in elderly patients are summarized and illustrated by a report of a 75-year old patient with CMV colitis. The clinical and pathologic features of CMV infections involving the gastrointestinal tract in noncompromised hosts are reviewed.

Clinically significant cytomegalovirus infections are usually found in patients in whom immunologic mechanisms have been altered or suppressed by neoplasia, chronic infections, or immunosuppressive therapy. They have been reported in bone marrow transplant recipients, in patients undergoing hemodialysis or extracorporeal circulation during open heart surgery and in association with gastrointestinal ulceration. Presented here is an unusual case of disseminated CMV infection with extensive involvement of the ileum and colon in an elderly adult with no underlying bowel disease, who had not received immunosuppressive therapy. The occurrence of CMV infections involving the gastrointestinal tract and the role of altered immunity in the elderly are reviewed.

CASE REPORT

A 75-year old white female was admitted to the UCLA Medical Center for evaluation of hypercalcemia on 29 November 1976. She had a history of hypertension for 40 years but had never received treatment. Six months prior to admission blood pressures as high as 200/110 mm. Hg. were noted. The hypertension responded to Aldomet®. She was also placed on a reducing diet and subsequently lost 13.5 kg. Approximately one month before admission she had been admitted to another hospital for evaluation of an episode of transient slurring of speech and epigastric discomfort. Serum calcium determinations at that time ranged from 8.3–14.8 mg./100 ml.; BUN was 29 mg.; creatinine, 2.9 mg.; uric acid, 12.3 mg./100 ml. Parathyroid hormone levels were reported to be twice normal. Upper gastrointestinal series, oral cholecystogram, barium enema, brain scan and electroencephalogram were within normal limits. An I.V.P. disclosed a probable cyst on the left kidney. The patient was discharged on Allopurinol, Colchicine and Aldomet but took only Aldomet regularly. One week before admission she developed mild abdominal cramping pain and diarrhea with six to eight liquid stools per day without fever, chills, hematochezia or melena.

On physical examination she was a moderately obese, elderly female. The blood pressure was 110/50 mm. Hg.; pulse, 80; respirations, 16; temperature, 36° C. Physical examination was within normal limits, except for Herberden's nodes and bilaterally decreased reflexes in the lower extremities.

Initial laboratory data included: Hgb., 10.2 gm.%; Hct., 30.5%; reticulocyte count, 2.8%; normal red cell indices; WBC, 12,800 with 63% neutrophils, 8% bands, 4% lymphocytes, 17% monocytes and 6% eosinophils. Creatinine was 2.5 mg.; BUN, 48 mg.; uric acid, 13.5 mg./dl.; SGOT, 41 I.U./l.; SGPT, 66 I.U./l.; alkaline phosphatase, 287 U./l.; serum calcium, 9.1 mg. (nl = 9.2-10.8); phosphorus, 3.2 mg.; PTH, 56 mEq./l. (nl = < 90); total protein, 5.1 gm.; albumin, 2.8 gm.; free T4

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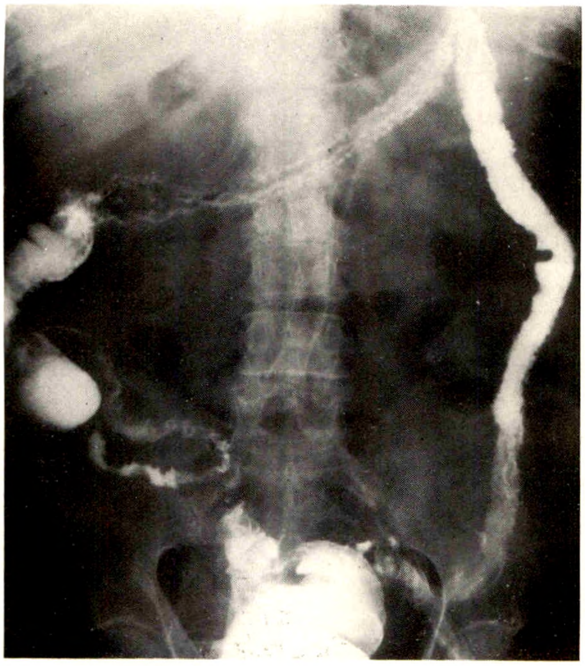

Fig. 1—Barium enema shows extensive mucosal ulceration throughout the colon with only rectal sparing.

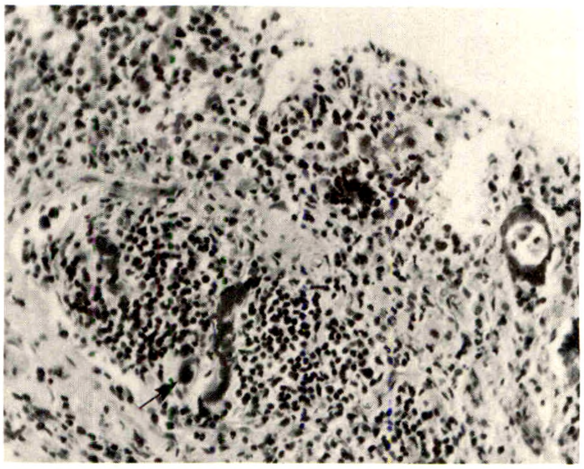

Fig. 2—Histologic specimen of terminal ileum showing mucosal ulceration, a dense chronic and acute leucocytic infiltrate and intracellular cytomegalic inclusion body (arrow) (Hematoxylin and eosin original magnification x125).

index, 2.7; T4 by RIA, 2.2 mcg./dl.; T3, 25 mg./dl.; TSH, 4.5 mcu./ml. (nl = 0-10). Serum iron was 19 mcg./dl.; iron-binding capacity, 114 mcg./dl and serum B_{12}, 1,824 picogm./ml. (nl = 330-1,025). The following laboratory studies were within normal limits: serum electrolytes, serum folate, a bone marrow and multiple sputum and urine cultures for AFB, stool cultures, serum protein electrophoresis and sigmoidoscopy. The gamma G and albumin were decreased on serum immunophoresis. Bone marrow examination revealed mild myeloid preponderance, normal iron stores and a few noncaseating granulomas which were negative for fungi, amyloid and AFB on direct stains. Chest x-rays showed diffuse symmetrical interstitial changes most consistent with interstitial pneumonitis. Stool examinations revealed moderate numbers of polymorphonuclear leucocytes and *dientamoeba fragilis* but no blood. A renal cyst was again detected on ultrasound. Skin tests were negative for tuberculosis, *candida* and streptokinase-streptodornase.

Initially, the patient continued to have five to ten liquid guaiac negative stools per day but on the 15th hospital day she passed 300 cc. of dark red blood per rectum. At gastroscopy two nonbleeding duodenal ulcers were visualized. Barium enema now revealed extensive mucosal ulceration involving the entire colon, except the rectum, most consistent with granulomatous colitis (Fig. 1). Although amebic colitis seemed unlikely, she was treated with a ten-day course of Flagyl. Intermittent brisk lower intestinal bleeding persisted throughout the remainder of the hospitalization. Inferior mesenteric arteriography was unsuccessful due to severe atherosclerotic changes. The patient became severely depressed on the 16th hospital day upon hearing that her husband had unexpectedly died. Several days later she had an inferior myocardial infarction complicated by congestive heart failure. On the 28th day she became febrile, hypotensive and developed right lower lobe rales. All cultures were negative and chest x-ray remained unchanged. Cefazolin, Gentamycin and Chloramphenicol were begun and Dopamine was administered for 48 hours. The patient had been receiving thyroid replacement, however, pituitary insufficiency was considered and hydrocortisone 250 mg. b.i.d. was begun two days before her death. The morning serum cortisol was later found to be normal. On the 31st day she began passing voluminous bloody stools. She was transfused and received 20 unit bolus therapy of intravenous pitressin with no response. As brisk bleeding continued, the patient and her family were made aware that a colectomy would be necessary for survival, however, surgery was firmly refused. Transfusions were finally terminated and on the 32nd hospital

TABLE I
CMV GASTROINTESTINAL INVOLVEMENT

Author	Patient	Clinical features	CMV involvement
Noncompromised hosts			
Dent[19]	31 yr. M	Diarrhea, weight loss, hypoproteinemia	Distal ileum (surgical specimen), autopsy performed.
Levine[22]	27 yr. F	Chronic gastric ulcer	Stomach—gastric ulcer
Possibly compromised hosts			
Henson[21]	79 yr. F	Polycythemia, subtotal gastrectomy	Stomach—ulcerated and nonulcerated mucosa
	18 yr. F	JODM*, septicemia	Stomach and duodenum—ulcerated and nonulcerated mucosae
	64 yr. F	AODM**, subtotal gastrectomy chronic gastric ulcer	Stomach—gastric ulcer

*Juvenile onset diabetes mellitus.
**Adult onset diabetes mellitus.

day, after two weeks of intermittent bleeding and 28 units of blood products, the patient expired.

PATHOLOGIC FINDINGS

At autopsy an area of hemorrhagic mucosa was seen in the distal jejunum and multiple discrete hemorrhagic erosions in the terminal ileum, cecum, ascending and transverse colon. Microscopic examination of these areas showed numerous epithelial cells with typical cytomegalic inclusions within the ulcer beds and surrounding submucosa. There was dense infiltration with both acute and chronic inflammatory cells. Inclusions were especially prominent in capillary endothelial cells. There were no granulomas in the bowel or in mesenteric lymph nodes (Fig. 2).

The alveolar septa of the lungs were diffusely thickened by vascular, fibrous tissue. Patchy lymphocytic infiltrates with rare cells with cytomegalic inclusions, consistent with chronic CMV interstitial pneumonitis were seen.

One of four identified parathyroid glands was three times normal size, with nodular hyperplasia on microscopic examination. The dentate nucleus was calcified, a characteristic cerebral finding of hyperparathyroidism. The thyroid gland showed chronic thyroiditis.

There was partial occlusion of the left renal artery with scarring and atrophy of the left kidney and microscopic bilateral nephrosclerosis.

The cause of death was exsanguination into the bowel from multiple colonic mucosal erosions consistent with CMV colitis.

COMMENT

General features of CMV infections:–Cytomegalovirus is a member of the herpes-virus group. Others include herpes viruses, types 1 and 2, Epstein-Barr virus and varicella-zoster virus. After an initial infection the genome of the virus persists in the host and may later spontaneously reactivate. This reactivation is characteristic of varicella-zoster and the herpes viruses but may also occur with CMV.[1] Immunoglobulin and autoimmune phenomena observed during some infections suggest that CMV may associate with human lymphocytes. Viral particles may also persist in renal tubular cells.[2] Viral antigen could therefore be transmitted by blood products as has been suspected, or by bone marrow or kidney transplants.[3–4] Recently, two research technics for detecting intracellular cytomegaloviral DNA fragments have been developed. One of these, anticomplement immunofluorescence, employs CMV antibodies which react with the viral antigen and fix complement. The other, cytohybridization involves *in situ* denaturation of cellular DNA and detection of the viral genome with a complementary tritiated DNA probe. These tests could be valuable for screening transplantation tissue and blood products given to immunosuppressed patients.[1, 2]

TABLE II

DISSEMINATED CMV WITH GASTROINTESTINAL INVOLVEMENT

Author	Patient	Clinical features	CMV involvement
Noncompromised hosts			
Tamura[25]	65 yr. M	Angioneurotic edema 6-wk. bloody diarrhea	Colon—ulcerated and nonulcerated mucosa, small intestine—ulcerated mucosa, lung, liver
Possibly compromised hosts			
Evans[16]	30 yr. F	Discoid *lupus*, diarrhea	Colon, liver, spleen
Nakoneczna[24]	71 yr. F	Pancytopenia, bilateral pneumonia, lower gastrointestinal bleeding	Rectum, lungs, kidney, thyroid, pituitary, uterus, adrenal, bone marrow
Henson[21]	18 yr. F	JODM*, pyelonephritis, septicemia	Stomach and duodenum, specific sites of dissemination not available
Spiegel	75 yr. F	HTN, mild azotemia, hyperparathyroidism, chronic thyroiditis, bloody diarrhea	Jejunum, ileum, cecum, ascending and transverse colon, lung

*Juvenile onset diabetes mellitus.

Adult CMV infections, although usually benign, have received increased recognition in recent years. In 1943 Hartz reported seven cases of adult disease.[5] By 1962 Wong and Warner had found only 55 cases in the world literature.[6] Fifty-four to eighty-one per cent of the adult population, however, harbors antibody titers.[7, 8] CMV is present on the cervix of normal women more frequently than herpes simplex type 2.[2] Jordan, et al, recently collected nine cases of a CMV mononucleosis-like syndrome over a ten-month period with diagnosis made by cultures of urine and oropharyngeal secretions.[9] Today CMV infections are recognized as a major cause of death in many bone marrow transplant units.

In 1977 Neiman reported a prospective study from the University of Washington of 80 bone marrow transplant recipients. There were 43 episodes of interstitial pneumonia, two-thirds of which were fatal. CMV was the most prevalent pathogen being isolated from 47% of the involved lungs.[10] Many aspects of this disease entity, such as the pathogenetic significance of cytomegalic inclusion bodies in single and multiple sites and the relationship of age and concurrent diseases to immune mechanisms, are poorly understood and clamor for more precise definition.

Pathologic characteristics:–Postmortem histologic evidence of infection by intranuclear and cytoplasmic inclusion bodies has been seen in 1% of random and in up to 51% of compromised host autopsies.[11–14] Frequent involvement is seen in lung, kidney, liver, adrenal, spleen, pancreas, large and small bowel. Detection of inclusion bodies on histologic specimens, however, is not a reliable indicator of presence of the virus. Macasaet isolated cytomegaloviruses from lung tissue in 6.8% of 502 unselected autopsies. Inclusion bodies were seen in only 26% of these cases.[15] Evans carefully searched tissues in 13 autopsies on adults with cytomegaloviral disease and found only three cases with infection localized to only one organ.[16]

The pathologic interpretation of CMV involvement in gastrointestinal lesions is difficult. CMV inclusion bodies are typical, rounded, eosinophilic, intranuclear or intracytoplasmic inclusions, which in the gastrointestinal tract are seen in endothelial and mucosal cells or fibroblasts surrounding ulcer beds. Vogel has shown that murine cytomegalovirus will preferentially localize to endothelial cells of granulation tissue.[17] If pre-existing or well-recognized gastrointestinal lesions are present with scattered CMV inclusions, the virus is labeled a secondary invader. If numerous inclusions are found with no recognizable underlying histology, the virus is thought to be a primary pathogen. There are flaws in this reasoning. The significance of seeing viral lesions is not fully understood, because many interactions occur at a cellular level. Another problem is the differentiation of CMV colitis from Crohn's colitis and ulcerative colitis. In CMV col-

TABLE III

LABORATORY FACTORS SUGGESTING ALTERED IMMUNE RESPONSIVENESS IN THE ELDERLY

Impaired delayed hypersensitivity skin-test reactions
Serum autoantibodies, such as: positive rheumatoid factor by latex fixation, antithyroid or antinuclear antibody
Elevated serum levels of Ig-G and Ig-A
Elevated erythrocyte sedimentation rate
Hyperglycemia
Hypoproteinemia
Azotemia
Iron deficiency

itis transmural inflammation, deep fissures and submucosal granulomas, features usually present in Crohn's disease are not seen. Only the presence of discrete ulcerations rather than diffuse involvement and small bowel involvement favor the diagnosis of CMV colitis over ulcerative colitis.

Gastrointestinal CMV infections:–In obviously immunosuppressed patients extensive gastrointestinal cytomegalic virus involvement is well documented. Goodman reported extensive and disseminated involvement in a patient who had received radiation therapy for a supposed lymphoma.[18] This case was labeled cytomegalic colonic vasculitis, because most inclusion bodies were within the endothelial cells and because these changes were unassociated with any other bowel pathology.

In patients taking corticosteroids cytomegalic inclusions are often found in pre-existing gastrointestinal lesions.[19–22] Henson has collected a series of ten patients with cytomegalic or *herpes simplex* inclusions surrounding gastrointestinal ulcers.[21] Three patients with gastrointestinal CMV inclusions were not receiving immunosuppressive therapy. Two of these patients had diabetes mellitus, one having also had a subtotal gastrectomy. The third patient had polycythemia and a subtotal gastrectomy. In two of these patients CMV inclusions were noted in ulcerated and nonulcerated musosae. Diabetics are felt to be predisposed to infections because of deficient macrophage mobility and phagocytosis, poor vascular perfusion and and hyperglycemia presenting a good substrate for microorganisms. Noncompromised hosts with CMV gastrointestinal involvement include Dent's case of diffuse ileal involvement and Levine's patient with CMV inclusions surrounding a chronic gastric ulcer.[19, 22] Cases of gastrointestinal CMV infections in all but obviously compromised hosts are listed in Table I.

Disseminated CMV infections:–Life-threatening disseminated cytomegalic involvement in the nonimmunosuppressed adult is rare. A 43-year old female with a seven-month history of myocarditis is reported by Waris.[23] Rising CMV titers were documented and urinary CMV inclusion cells were found. She developed adrenal insufficiency and was given 10 mg. of prednisolone daily. At autopsy the myocardium and adrenal had cytomegalic viral inclusions. Evans has reported cases of scattered organ involvement in patients with diabetes, renal failure, myxedema and bladder carcinoma.[16] These patients most likely represent immunocompromised hosts.

The case reported in this paper represents the unusual findings of disseminated CMV infection with extensive gastrointestinal involvement in an elderly host not on immunosuppressive agents. There are three similar reports of patients, who were probably immunocompromised (Table II). Nakoneczna describes a 71-year old emaciated female with nausea and vomiting who had a white blood cell count of 2,100 with 30% polymorphonuclear leucocytes, 69% lympohocytes, 1% monocytes and 70,000 platelets.[24] Most likely this patient with 630 granulocytes was not immunologically competent. Evans' case of a 30-year old female with a 12-year history of discoid *lupus*, expired following a two-week course of severe diarrhea.[16] Multiple CMV inclusions were found in the colon with several inclusions in the liver and spleen. An apparently noncompromised 65-year old male with a six-week course of severe bloody diarrhea was cited by Tamura.[25] At autopsy a large number of cytomegalic inclusions were noted in colonic ulcer margins and bases and in endothelial cells. Scattered inclusions were present in the lungs and rare ones in the liver (Table II).

Factors influencing immunocompetency in the elderly:–It is well known that increased age is associated with a decline in cell-mediated and humoral immunity. Elderly patients also have an increased incidence of neoplasia, autoimmune phenomena and certain infections, as gram nega-

TABLE IV

ALTERED IMMUNE RESPONSIVENESS PREDISPOSING CONDITIONS

1. *Immunologic diseases*
   - Immune deficiency syndromes such as:
     - Idiopathic late-onset immunoglobulin deficiency
     - Chronic mucocutaneous candidiasis
2. *Hematologic diseases*
   - Lymphoproliferative diseases such as:
     - Leukemia
     - Lymphoma
     - Multiple myeloma
   - Thymoma
   - Asplenia
   - Iron deficiency anemia
3. *Oncologic diseases*
   - Nonlymphoid malignancies
4. *Autoimmune diseases*
   - Systemic *lupus erythematosus*
   - Rheumatoid arthritis
   - Polyarteritis
   - Other disorders such as:
     - Thyroiditis
     - Pernicious anemia
     - Idiopathic Addison's disease
5. *Endocrinopathies*
   - Diabetes mellitus
   - Hypothyroidism
   - Cushing's syndrome
   - Estrogen excess states
6. *Infections*
   - Viral infections such as:
     - Varicella-zoster
     - Rubella
     - Rubeola
     - Epstein-Barr
     - Cytomegalovirus
   - Bacterial infections such as:
     - Tuberculosis
     - Leprosy
     - Syphilis
   - Mycotic infections such as:
     - Blastomycosis
     - Coccidioidomycosis
   - Parasitic infections such as:
     - Schistosomiasis
     - Toxoplasmosis
7. *Drug-induced*
   - Immunosuppressive chemotherapy
   - Radiation therapy
   - Corticosteroids
   - Large dose estrogen
8. *Miscellaneous*
   - Senesence
   - Protein-losing states such as:
     - Nephrotic syndrome
     - Exfoliative dermatitis
     - Severe burns
     - Intestinal lymphangiectasia
   - Protein-calorie malnutrition
   - Renal failure
   - Sarcoidosis

tive bacteremia.[26] Our patient was 75 years old, anergic, had chronic thyroiditis and a parathyroid adenoma.

Numerous studies in man have documented impaired immunologic responsiveness in the elderly. Howells found that residents of an old people's home developed lower antibody titers in response to an influenza vaccine than did a younger population.[27] Upon testing cell-mediated immunity by delayed hypersensitivity skin tests, lymphocyte responsiveness to phytohemagglutinin and T-cell dependent Ig-G response to flagellin, Roberts-Thompson and other investigators have found less responsiveness in people over 60 years old compared to those under 25 years old.[28, 29] Patients over 80 years old also had increased mortality with greater impairment of immune responses.[28]

A higher incidence of autoantibodies has also been noted in older individuals.[30] Hallgren found a positive rheumatoid factor, antithyroid and antinuclear antibodies in 20-40% of an elderly population compared to 0-29% of individuals 20-25 years of age.[31] Elevated erythrocyte sedimentation rates and serum Ig-G and Ig-A levels are also present in healthy elderly humans (Table III).[32–34] No direct correlation has been demonstrated between serum immunoglobulin levels, sedimentation rates, or autoantibody titers in these patients.[32, 33] Hallgren has noted, however, a frequent occurence of decreased lymphocyte phytohemagglutinin responsiveness in patients with autoantibodies.[31] This finding is consistent with the clinically recognized occurrence of autoimmune diseases in patients with immunodeficiences, as chronic mucocutaneous candidiasis and idiopathic late-onset immunoglobulin deficiency.[35,36] Neoplasias also develop more frequently in immunodeficient patients.[37]

Age-related declines in immune functions in mice have been extensively studied. Some strains of mice with a short life span have a high incidence of autoimmune phenomena. Fernandes demonstrated marked impairment of T-cell responses in the autoimmune-susceptible strains.[38] In autoimmune-susceptible and normal mice, Pachciarz induced a more rapid decline in T-cell function with a thymectomy or radiation, suggesting that thymic function as well as stem cell production is important to maintain T-cell function.[39] After reviewing the literature and applying hypothetical models, Stoltzner concludes that both cellular differentiation and proliferation are important during aging to maintain lymphocyte function.[40]

Endocrine abnormalities may also influence immunocompetency. Experimental hypothyroidism is accompanied by a slight decrease in weight of lymphatic organs. On the other hand, hyperparathyroidism and hypercalcemia may stimulate some immune phenomena.[41]

Certain infections produce anergy, or impaired immunologic reactivity to other antigens. T-cells and macrophages from infected, anergic animals function normally when transferred to healthy animals. Thus it is postulated that a subpopulation of lymphocytes may suppress normal lymphocyte function.[42] This occurs in chronic infections as syphilis, tuberculosis, leprosy, chronic mycoses and in viral infections with rubeola, rubella, varicella-zoster and Epstein-Barr viruses.[42–44] Recent studies suggest that CMV infections may also impair immune defenses. Howard demonstrated that skin graft survival was significantly prolonged in mice infected with CMV on the day of or five days prior to grafting.[45] Hamilton found 80-100% mortality in mice injected with murine CMV and an inoculum of *Pseudomonas aeruginosa, Staphylococcus aureus,* or *Candida albicans.* Mice previously immunized to CMV and given the same inoculum had no mortality.[46] Thus, the patient with CMV infection may be less able to suppress a concomitant fungal or bacterial infection.

Other diseases found in the elderly which may alter immune responsiveness include diabetes mellitus, renal failure, autoimmune disorders, iron deficiency anemia, protein-calorie malnutrition, thymoma and protein-losing states as the nephrotic syndrome, burns and exfoliative dermatitis (Table IV).[47–49]

Impairment of immune mechanisms especially in the elderly are often unrecognized. It should be emphasized that elderly patients have impaired immune defenses and may be unsuspected hosts of opportunistic infections. In such patients disseminated CMV infections may extensively involve the gastrointestinal tract and result in severe lower intestinal bleeding.

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CLINICAL VIGNETTE

Choriocarcinoma of the Stomach

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A 23-year old woman with primary choriocarcinoma of the stomach presented with abdominal pain and massive hepatomegaly. Serum levels of CEA and serum and urine levels of β-HCG were markedly elevated. Immunoperoxidase staining for CEA and HCG reveal both to be present in morphologically typical carcinoma cells. This suggests that serum β-HCG may be a useful tumor marker of gastric carcinoma.

INTRODUCTION

The most common malignant neoplasms that occur in the stomach are carcinoma, lymphoma and less commonly plasmacytomas, sarcomas and carcinoids.[1] Choriocarcinoma has been reported to arise, rarely, within an adenocarcinoma of the stomach.[2–14] This communication reviews this unusual neoplasm, emphasizing the use of β-human chorionic gonadotrophin (β-HCG) as a diagnostic marker of gastric carcinoma. Although other workers[15, 16] have documented elevated serum β-HCG levels in patients with gastric carcinoma, we report here the first demonstration of HCG within morphologically typical gastric carcinoma cells by immunoperoxidase staining.

CASE REPORT

A 23-year old black Bahamian woman was well until two months prior to admission when she developed a flu-like syndrome. During the subsequent two months she developed malaise, anorexia, night sweats and fever with a 11.25 kg. weight loss. Two weeks prior to admission she began to have sharp, constant right upper quadrant pain and nausea with no other gastrointestinal symptoms.

Physical examination revealed a wasted woman, appearing chronically ill, with a temperature of 39.8° C. She had scleral icterus and pale conjunctivae. Her abdomen was protuberant with active bowel sounds. Her liver filled the upper two-thirds of the abdomen with a total span of 23 cm.; it was hard and nodular. The rectal examination was normal except for brown hematest positive stool. Neurological and pelvic examinations were unremarkable.

Laboratory data included: Hgb., 6.4 gm./dl.; Hct., 21.6%; WBC, 5,800/cu. mm. Chest x-ray revealed an elevated right hemidiaphragm and liver scan showed massive hepatomegaly with numerous filling defects. An upper gastrointestinal series (Fig. 1) revealed an ulcerated mass which, on endoscopy, appeared irregular and ulcerated and involving the lesser curvature from the antrum to the mid fundus. Endoscopic biopsies of this mass revealed bizarre multinucleated giant cells suggestive of choriocarcinoma, which initially were thought to be metastatic to the stomach from the genital tract. Serological studies included CEA level, 79 ng./ml.; urinary (Gravidex) HCG, 355,000 MIU/ml.; serum β-HCG, 155,000 MIU/ml. and cerebrospinal fluid HCG of 1,430 MIU/ml. She was treated with radiation therapy as well as intravenous actinomycin-D and 6-mercaptopurine mistakenly directed at a choriocarcinoma metastatic from the genital tract. She had a rapid downhill course and expired.

From the Divisions of Gastroenterology and Pathology, University of Miami, School of Medicine, Jackson Memorial Hospital and the Miami Veterans Administration Hospital.

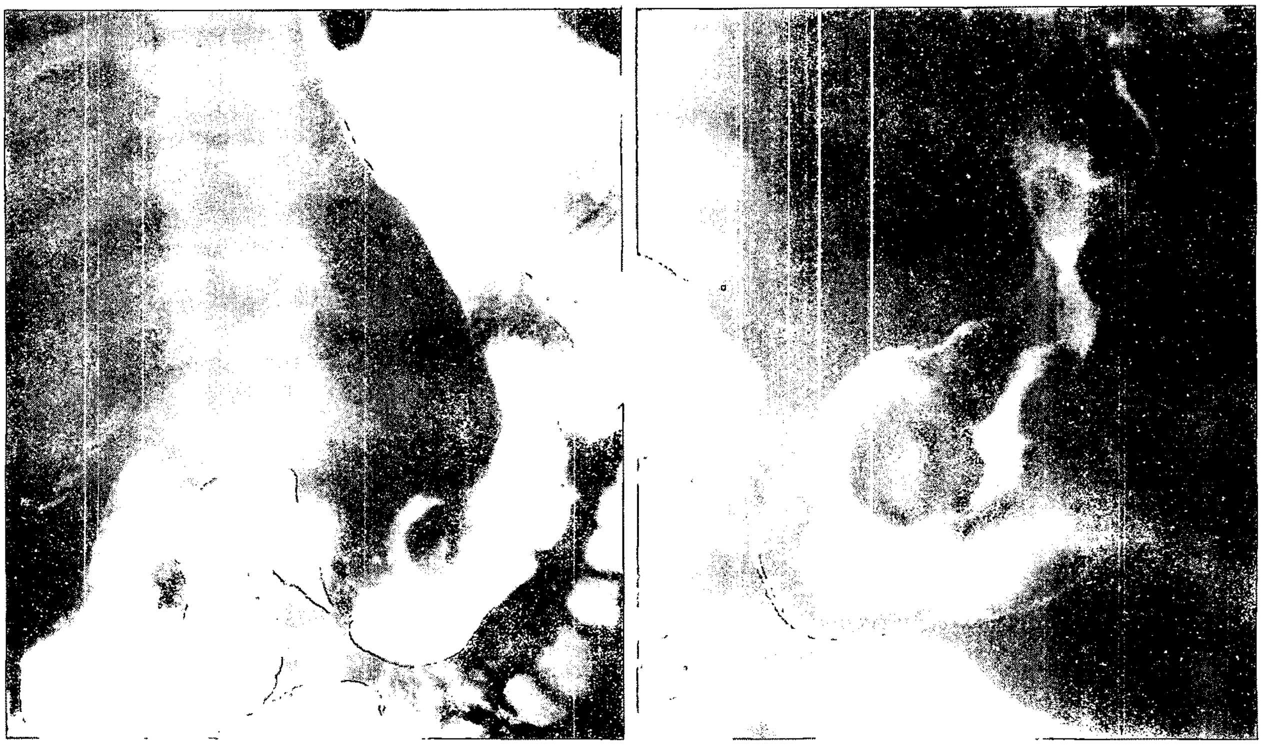

Fig. 1—Two views of ulcerated antral tumor mass.

PATHOLOGY

Postmortem examination revealed a gastric tumor, measuring 10.5 × 6 × 2 cm. located along the lesser curvature which had diffusely infiltrated the gastric mucosa and *muscularis*. The mucosa was generally intact, except for two large ulcers located in this tumor mass. Metastatic foci were found on the lesser curvature of the stomach, superior pancreatic and hilar lymph nodes, as well as on the liver which weighed 5,000 gm. The lung contained a solitary 1 cm. metastasis. Meticulous examination of the uterus and its adnexae failed to reveal a tumor but the ovaries contained numerous *corpus luteum* cysts and the endometrium was thick and focally hemorrhagic.

The microscopic structure of the gastric tumor revealed areas of carcinoma with variable levels of differentiation. Glandular structures were formed in some areas and other portions contained signet ring cells. Many of the adenocarcinoma cells were mucicarmine positive. The obvious adenocarcinoma cells were negative for acid and alkaline phosphatases and contained no dystrophic calcification. The metastatic lesions in lymph nodes and the pulmonary metastasis also were morphologically carcinoma.

The choriocarcinoma component in the tumor was recognized by its greater pleomorphism, presence of syncytial malignant giant cells and marked angioinvasiveness (Figs. 2 and 3). Extensive areas of necrosis were present, within and around which dystrophic calcification was found. Some of the malignant cells contained alkaline (but not acid) phosphatase. The metastases to the liver were of trophoblastic type exclusively.

Morphologically transitional forms of cells were present so that a sequence of carcinoma to choriocarcinoma could be traced.

Immunoperoxidase stain of the gastric tumor for CEA was performed for us by Goldenberg[15] (Fig. 4) revealing that the CEA marker, found with typical gastric carcinoma, was primarily limited to the mononuclear carcinoma cells. Kurman and Tabei performed an immunoperoxidase stain for HCG (Fig. 5) showing a dense reaction also in the mononuclear tumor cells rather than the bizarre multinucleated giant cells. No sharp distinction be-

Fig. 2—Photomicrograph—gastric biopsy—choriocarcinoma (Ch) cells invading a large vein and less cellular carcinoma (Ad) cells in the same section.

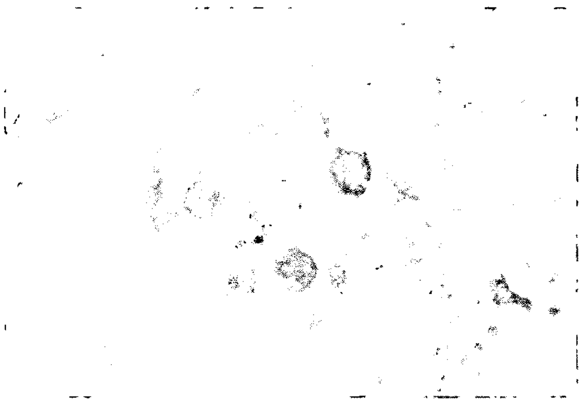

Fig. 3—Gastric biopsy—bizarre multinucleated giant cell with trophoblastic characteristics.

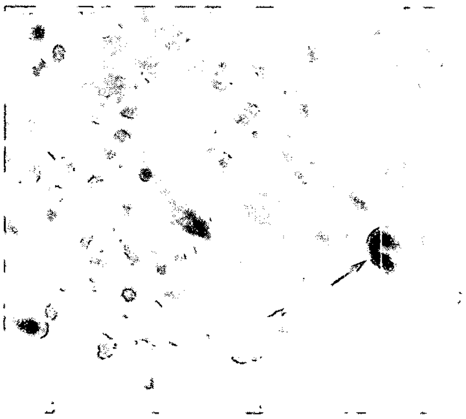

Fig. 4—Immunoperoxidase stain for CEA—the label primarily confined to mononuclear cells (arrow).

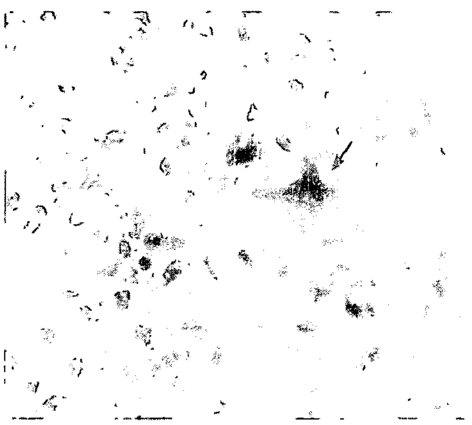

Fig. 5—Immunoperoxidase stain for HCG—the label primarily confined to mononuclear cells (arrow).

tween carcinoma and trophoblastic elements, however, was possible on the basis of immunoperoxidase stains alone.

COMMENT

The term primary choriocarcinoma of the stomach is a misnomer. Pick,[9] in 1926, first suggested that the development of trophoblastic elements in gastric cancer represents a dedifferentiation of adenocarcinoma cells to the level of embryonal trophoblast. Support for this view, in that comes from observations, as seen in this patient, that these tumors usually have mixed carcinomatous and trophoblastic elements. In 18 previously reported cases[14] both trophoblastic and carcinoma cells were found either in the primary gastric lesion or in the metastases. In those cases where mixed adeno- and choriocarcinoma were present in the primary gastric lesion, there was a strong tendency for pure adenocarcinoma to metastasize to regional lymph nodes, as is typical for this tumor. The trophoblastic elements, however, tended to metastasize via the hematogenous route to the liver and lungs, as is typical for genital choriocarcinoma. Further support for the thesis that trophoblastic elements arise in a pre-existing gastric adenocarcinoma comes from epidemiologic data including similar age and sex distributions for gastric adenocarcinoma and choriocarcinoma, as well as an increased incidence of gastric choriocarcinoma in Japan, where the incidence of adenocarcinoma is also high.[12] Regan and Cremin,[10] in 1960, suggested that the occasional absence of adenocarcinoma cells is due to the far shorter doubling times of choriocarcinoma compared to adenocarcinoma.

This report emphasizes that the dedifferentiation of carcinoma cells to trophoblastic tissue results in cells capable of producing HCG. Furthermore, immunoperoxidase staining of this tumor revealed that the CEA marker,[15] found with typical gastric carcinoma, is primarily limited in these tumors to carcinoma cells. Far more intriguing are two reports of HCG detection in typical gastric carcinomas without recognized trophoblastic elements.[16, 17] Possibly the failure to recognize "trophoblastic" (HCG-producing) cells was due to the limitations posed by conventional light microscopy. In another report,[19] serum HCG levels in nontrophoblastic gynecologic tumors did not correlate well with radical surgical removal of the tumors.

In this case, immunoperoxidase staining for HCG showed a dense reaction in the mononuclear tumor cells morphologically typical of gastric carcinoma. As shown here and in other reports, elevated serum levels of HCG may occur in malignant and nonmalignant conditions other than of genital trophoblast origin. The clinical applicability of radioimmunoassay for β-HCG as a tumor marker for gastric cancer requires further study.

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CLINICAL VIGNETTE

Periportal Hepatic Necrosis in Reye's Syndrome

ONE CASE IN A REVIEW OF EIGHT PATIENTS

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Hepatic necrosis, usually periportal and mild but occasionally of significant extent, is described in the liver of patients with Reye's syndrome, in addition to diffuse microvesicular fatty change. Review of clinical and pathologic findings of eight cases of Reye's syndrome diagnosed between 1970-1978 showed extensive peripheral lobular necrosis of hepatocytes in one case. Other than biochemical evidence of greater liver damage, the latter case showed no significant differences in clinical and laboratory findings from the seven cases with diffuse fatty change of hepatocytes but no liver cell necrosis. The significance of this periportal hepatic necrosis is discussed in the light of current theories concerning the etiology and pathogenesis of Reye's syndrome.

INTRODUCTION

In addition to diffuse microvesicular fatty change, mild degrees of hepatic necrosis have been described in the livers of patients with Reye's syndrome.[1-3] This hepatic necrosis is often periportal in distribution[4-7] and occasionally of significant extent.[8] Histopathological review of liver tissue from eight cases of Reye's syndrome diagnosed at the Milton S. Hershey Medical Center between 1970 and 1978 showed extensive peripheral zonal necrosis in only one. Clinical data were reviewed in an attempt to assess any differences in the clinical and laboratory findings which might correlate with this infrequently described histopathological change.

MATERIALS AND METHODS

Review of medical and pathology records of all patients less than 16 years of age coded as encephalitis, encephalopathy, cerebral edema, hepatic necrosis and/or fatty liver revealed eight cases which conformed to the clinicopathologic entity of Reye's syndrome.[4] Autopsy liver tissue in six instances and three needle liver biopsies from two patients who survived, were examined. Formalin-fixed paraffin embedded sections were stained with hematoxylin and eosin, periodic-acid Schiff with and without diastase, Sudan Black, Gordon and Sweet's silver impregnation technic for reticulin and Masson's trichrome. Frozen sections of formalin-fixed hepatic, renal, cardiac and pancreatic tissue were stained with Oil Red O. Hematoxylin and eosin stained sections of brain were reviewed. Clinical data obtained from patients' charts were correlated with histopathological findings.

RESULTS

The salient clinical features and laboratory findings in our eight cases with Reye's syndrome are shown in Tables I and II. All the children were white. None had a history of toxin or drug exposure, although Case 6 had a serum salicylate level of 37 mg./dl. (normal 4-25 mg./dl.). The grade of encephalopathy was determined according to Schubert, et al.[9] Absence of hypoglycemia reflects therapeutic intervention prior to admission to Hershey Medical Center. Serum bilirubin levels on admission ranged from 0.3-1.4 mg./dl. (normal 0.1-1.2). Histopathological findings are summarized in Table III, graded + (mild), ++ (moderate) and +++ (severe). In Case 1, there was prominent hemorrhagic periportal necrosis (Figs. 1 and 2)

From the Department of Anatomic Pathology, Milton S. Hershey Medical Center of the Pennsylvania State University.

TABLE I

Clinical Data in Eight Patients with Reye's Syndrome

Case sex/ age (yr.)	Clinical presentation	Grade of encephalopathy		Exchange Transfusions	Outcome
		On admission	Peak		
1/M/11	Headache, rhinitis, 3-5 days, fever, vomiting.	3	5	4 +hemodialysis	Died 4 days after admission.
2/M/12	Cough, chest congestion, 6 days, fever, vomiting.	3	5	6	Died 11 days after admission.
3/F/14	Upper respiratory tract infection, 5 days. vomiting 2 days, fever.	3	5	1	Died 16 hours after admission.
4/M/2	Fever 3 weeks, vomiting, lethargy, seizures.	3	5	0	Died 3½ hours after admission.
5/F/5	Upper respiratory tract infection, fever, vomiting 3½ days.	4-5	5	1	Died 6 days after admission.
6/F/8	Chest cold 4 days, fever, vomiting.	2	5	1	Died 2 days after admission.
7/F/5	Upper respiratory tract infection, fever, vomiting, 2 days, delirious, unresponsive	3		2	Discharged well 7 days after admission.
8/F/3	Cough 3 days, fever, seizures	4		3	Discharged with residual cerebellar ataxia 19 days after admission.

TABLE II

Laboratory Data in Eight Patients with Reye's Syndrome

Case	Peak serum NH_3 (20-50 ug./dl.)	Peak SGOT (5-40 U./l.)	Peak SGPT (5-30 U./l.)	Admission serum glucose (70-120 mg./dl.)	Prothrombin time (9.2-12.8 sec.)	Cerebrospinal fluid values
1	830	3,030	3,570	98	37.7	Bloody tap
2	370	> 300	199	184	19.6	Within normal limits
3	567	243	—	98	18.5	Within normal limits
4	82	378	56	93	19.4	Within normal limits
5	920	440	574	124	23.2	Within normal limits
6	396	> 300	120	108	18.9	Within normal limits
7	260	395	—	25	15.5	Within normal limits
8	140	258	39	90	11.6	Within normal limits

confluent between portal tracts and a mild mixed portal and periportal inflammatory infiltrate. Remaining hepatocytes showed severe microvesicular fatty change. Moderate centrilobular cholestasis was noted. No other case showed either hepatic necrosis on inflammation. Cases 1-5 had cerebral edema with diffuse anoxic-ischemic neuronal changes.

COMMENT

The eight patients described show most of the clinicopathological features of Reye's syndrome. All had an antecedent upper or lower respiratory tract viral-like infection, followed by fever, vomiting and encepahlopathy. In none could drugs or toxins be implicated. All had normal cerebrospinal fluid values, raised serum ammonia levels, abnormal liver tests and fat accumulation in the liver and other viscera. Case 1, in addition, showed prominent hemorrhagic periportal necrosis previously reported in five patients by Brown and Ishak.[8] Microvesicular fatty change of remaining centrilobular and mid zonal hepatocytes and minimal inflammatory response is consistent with Reye's syndrome rather than with phosphorus poisoning. The clinical presentation, treatment and progress in Case 1 were similar to those of Cases 2-6, all of whom also subsequently died, except for an episode of hemodialysis and higher serum transaminase levels and prothrombin time in Case 1. The

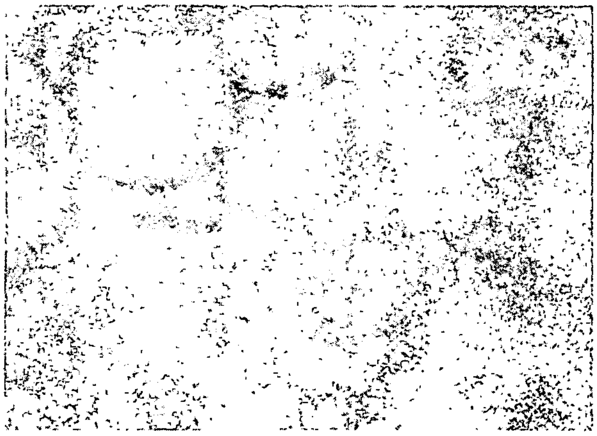

Fig. 1—Case 1. Hemorrhagic periportal hepatic necrosis (Hematoxylin and eosin, original magnification x50).

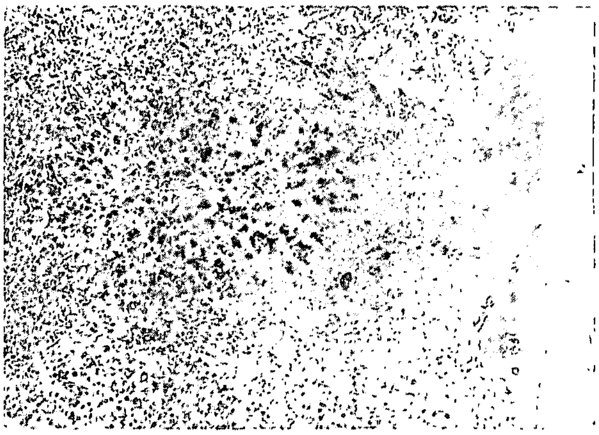

Fig. 2—Case 1. Periportal hepatic necrosis (Hematoxylin and eosin, original magnification x150).

TABLE III
HISTOPATHOLOGICAL FINDINGS IN EIGHT PATIENTS WITH REYE'S SYNDROME

	Liver					Fat accumulation in		
	Steatosis							
Case	H & E	Oil Red O	Glycogen depletion	Necrosis	Canalicular cholestasis	Heart	Kidney	Pancreas
1	+++ centrilobular mid zonal	+++ centrilobular mid zonal	++ centrilobular mid zonal	+++ periportal, hemorrhagic	++ centrilobular	+++	+	+++
2	++ diffuse especially centrilobular	+++ diffuse, centrilobular and mid zonal accentuation	++ mid zonal	—	+ centrilobular	+++	++	+++
3	++ diffuse	+++ diffuse	+++ diffuse	—	+	+++	+++	++
4	—	+++ diffuse	+++ diffuse	—	—	+++	+++	+
5	+ diffuse	+++ diffuse	++ diffuse, periportal accentuation	—	++ centrilobular, mid zonal	+	+	—
6	+++ diffuse		++ diffuse	—	—			
7	+++ diffuse	+++ diffuse	—	—	—			
8	—		—	—	—			

+ mild, ++ moderate, +++ severe

latter values probably reflect the greater degree of liver damage. The two patients who survived (Cases 7 and 8) seem to have had antecedent symptoms of shorter duration and lower serum ammonia levels than those who died. Glasgow, et al[10] showed that survival was related to low initial levels of blood ammonia. Neither survivor had hepatic glycogen depletion, associated with a bad prognosis.[7] Case 8 had less deranged liver function, an apparently normal liver in hematoxylin and eosin stained sections and fatty change in periportal hepatocytes in Giemsa stained sections.[11]

The etiology and pathogenesis of Reye's syndrome are controversial. It has been suggested that there is a primary hepatic disturbance with secondary dysfunction of other organs. Ammonia intoxication, as also occurs in patients receiving ammonia loads or with enzymatic defects in the urea cycle, has a toxic effect on the brain.[10] Although a raised serum ammonia level is a contributing factor to the encephalopathy, hypoglycemia and accumulated metabolites or exogenous toxins in the serum also probably play a role. Occasionally patients regain consciousness after intravenous glucose.[10] Exogenous agents such as aflatoxin, salicylates, pentenoic acid, pesticide chemicals and hypoglycin may increase lethality of subsequent viral infection (especially influenza B or varicella) by impairment of normal immune mechanisms[12, 13] or as a trigger to underlying urea cycle enzyme deficiencies in susceptible individuals.[14] Whether the latter defects in ammonia metabolism are inherited or induced is unknown. The fact that Reye's syndrome is rarely recurrent militates against a genetic predisposition.[12]

Occasionally encephalopathy develops in Reye's syndrome before there is biochemical or histological evidence of hepatic dysfunction, suggesting that the brain is directly involved.[15–17] A common mitochondrial insult compromising energy-dependent systems seems most likely.[12, 18] Mitochondrial ultrastructural changes of matrix expansion, loss of dense bodies and bizarre pleomorphic shapes[19, 20] are described in liver, brain, heart and pancreas. Repeat liver[14] and brain[20] biopsies in survivors are normal, indicating minimal light microscopical structural damage. Two months after the acute episode, Case 7 showed mild residual steatosis and hepatocyte regeneration.[7] A transient decrease in hepatic carbamyl phosphate synthetase and ornithine transcarbamylase (urea synthesizing enzymes unique to mitochondria) and in cytochrome oxidase and succinic dehydrogenase (mitochondrial enzymes involved in electron transport) is found.[21] An uncoupling factor, other than fatty acids, in the serum of patients with Reye's syndrome results experimentally in generalized mitochondrial damage.[18] A mitochondrial insult would limit the ability of a cell to oxidize fatty acids, ketone bodies and pyruvate, thereby necessitating an acceleration in glycolysis to meet tissue energy demands.[12] Hepatic glycogen depletion is frequently present and often exhibits periportal accentuation.[7] All our patients who died had moderate to severe hepatic glycogen depletion in autopsy liver tissue. The two who survived showed no glycogen depletion of hepatocytes in percutaneous liver biopsies. Depressed hepatic ATP, however, is not demonstrated.[21]

Although fatty change in the liver lobule in Reye's syndrome is diffuse, early changes[7, 15–17] or more severe damage with necrosis[4–8] are usually periportal, an area less susceptible to anaerobic insults than the centrilobular zone. Brown and Ishak's[8] hypothesis that fatty acids may be the potential toxin causing mitochondrial injury and especially of periportal hepatocytes may have validity because these liver cells are the first to be exposed to high levels of fatty acids and are less capable of metabolizing fatty acids as compared with centrilobular hepatocytes. Aflatoxin B also causes periportal hepatic necrosis in rats. Our Case 1 had "hemorrhagic" periportal necrosis which Brown and Ishak[8] suggest is due to the toxic effect of fatty acids on sinusoidal endothelial cells.

Although the etiology of Reye's syndrome may be multifactorial, there is increasing evidence that a circulating toxic substance may be involved in its pathogenesis. Our case with extensive peripheral lobular hepatic necrosis further supports the idea of periportal hepatocytes being subjected to the highest concentrations of this circulating toxin.

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CLINICAL VIGNETTE

Idiopathic Intrahepatic Cholestasis of Pregnancy

REPORT OF AN UNUSUAL CASE AND REVIEW OF THE RECENT LITERATURE

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An atypical case of idiopathic cholestasis of pregnancy occurring in the 16th week of gestation in a 24-year old Pakistani female is presented. The case is unusual both in the duration of the jaundice as well as in the high levels of bilirubin found in the presence of normal renal function. A review of the recent literature emphasizes that this disorder is not entirely benign for the mother and the fetus. It also discusses some of the alterations in estrogen and lipid metabolism that are seen, as well as the possible mechanisms responsible for the increased incidence of gallstone formation found in these patients.

INTRODUCTION

Jaundice is a relatively rare complication of pregnancy occurring in anywhere from 1 in 1,500[1, 2] to 1 in 2-3,000[3] cases depending on the series. Excluding viral hepatitis, the primary cause is recurrent cholestasis of pregnancy, a syndrome characterized by pruritus and mild jaundice due to intrahepatic cholestasis which tends to recur in subsequent pregnancies or upon use of oral contraceptive agents. The entity was recognized by Ahlfeld in 1883 but has been well-described only in the past 25 years, chiefly through the work of the Scandanavians Thorling[4] and Svanborg.[5] The following documented case of cholestasis of pregnancy is atypical in several aspects and suggests that previously reported descriptions of the syndrome may have to be revised.

CASE REPORT

A 24-year old pregnant Pakistani female was admitted to the Queens Hospital Center (QHC) for the first time on 12 October 1976 because of pruritus and jaundice. Her last menstrual period was on 19 May 1976 and this was her second pregnancy. Her first pregnancy had been voluntarily terminated at six weeks of gestation in February, 1976; there was no history of pruritus or jaundice during that pregnancy. She was first seen at the QHC Out-Patient Department in August, 1976; her only complaint at that time was morning sickness. At approximately the 15th week of pregnancy she developed generalized pruritus, followed in one week by the onset of jaundice. She had no prior history of liver disease and was taking no medications. There was no significant past medical history. She denied alcohol use or exposure to hepatotoxic agents. There was no history of prior use of oral contraceptives.

At the time of admission she was afebrile. The pertinent physical findings included jaundice, skin excoriations and a firm, nontender smooth liver that was 6 cm. below the costal margin with a total span of 16 cm. in the mid clavicular line. There was no splenomegaly and there were no stigmas of chronic liver disease. No spider angiomas were noted.

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TABLE I

	9/29	10/13	10/14	10/18	10/22	11/5	11/13	12/10	12/14	12/30	2/1	2/16	3/18
SGOT	56	43	38	41	34	29	—	51	—	50	47	39	93
Alkaline phosphatase	225	277	279	342	266	278	298	305	350	475	535	208	350
Total bilirubin	9.3	10	23	17.8	13.5	19.2	18.1	24.7	29.4	35.5	27.5	9.8	2.4
Direct bilirubin	—	—	—	12.2	9.2	—	11.4	14.4	19.5	22.8	19.8	—	—
Cholesterol	300	335	346	332	235	281	—	390	260	322	321	202	292
Total protein/ albumin	—	6.7/3.7	6.7/3.4	7.2/—	6.5/2.8	5.7/2.6	—	6.9/3.4	6.4/3.4	—	6.4/2.7	4.4/1.9	7.5/4.5

Laboratory values at the time of admission included a hemoglobin of 10.5 gm and a normal white blood cell count. Serum bilirubin was 23 mg.% with an alkaline phosphatase of 277 I.U. (normal 45-115); SGOT of 43 units and cholesterol of 355 mg.%. The hepatitis B antigen was repeatedly negative. By the fifth hospital day her total bilirubin had fallen to 17.8 mg.% with a direct of 12.2 mg.% (Table I). The prothrombin time was 11.1 seconds with a control of 11.0 seconds while her serum amylase was 106 units. Serum haptoglobin was 130 mg.%; her Coombs test and cold agglutinins were negative; latex fixation was 1:100; G-6-PD levels were normal. Chest x-ray was normal while abdominal ultrasound failed to reveal any evidence of gallstones, dilated biliary tree or pancreatic enlargement. Except for her itching, however, she felt well and she left the hospital after a two-week stay on cholestyramine therapy.

She was readmitted one week later complaining of acute and severe right upper quadrant pain radiating to the right flank. For one week in the hospital, pain recurred several times and was associated with an increase in total bilirubin to 20.6 mg.% (direct: 13.6 mg.%) and an alkaline phosphatase of 299 I.U. This pain had not been present before. She underwent exploratory laparotomy for presumed biliary tract disease and was found to have a normal gallbladder and a normal biliary tree with no evidence of gallstones. A liver biopsy (Fig. 1) was obtained at surgery and revealed well preserved liver architecture, severe centrilobular cholestasis and bile thrombi in central and peripheral bile canaliculi. No evidence of acute or chronic hepatitis or extrahepatic obstruction was seen. Orcein stains failed to show Australia antigen.

Electron microscopy revealed dilated bile canaliculi between liver cells. The canaliculi were filled with granular and membraneous biliary material. There was marked loss of canalicular microvilli (Figs. 2 and 3). Many hepatocytes showed nonspecific changes, e.g. irregular and enlarged mitochondria with crystaline inclusions and free ribosomes dispersed throughout the cytoplasm. Viral particles were not identifiable.

A diagnosis of intrahepatic colestasis of pregnancy was made.

Postoperatively the patient remained icteric. She was discharged on the eighth postoperative day and followed as an outpatient where her bilirubin peaked at 35.5 mg.% with a direct fraction of 19.5 mg.%. She was readmitted with prodromal labor on 11 February 1977 and delivered a jaundiced female baby two days later.

The baby was born at the 36-37th week of gestation, was meconium-stained and had a greenish-yellow color at birth. The infant weighed 2.461 g.; was 49 cm. long and had an apgar score of 8 at one minute and 9 at five minutes. Except for early postnatal hypoglycemia (blood glucose 20 mg.) and hyperbilirubinemia (18.2 mg./with 7.5 mg. direct) at 32 hours of age, all other studies including hepatitis associated antigen, monospot test, α-1 antitrypsin levels, serum protein electrophoresis, G-6-PD levels and VDRL were normal. The initial hyperbilirubinemia in the infant slowly subsided over the next three weeks as did the high alkaline phosphatase levels which peaked at 880 I.U. and then came down to 350 I.U. at the time of discharge on 7 March 1977. Serum bile acid and Ig-M levels were elevated in the baby's blood. At the time of discharge the infant weighed 3.25 kg. and discharge

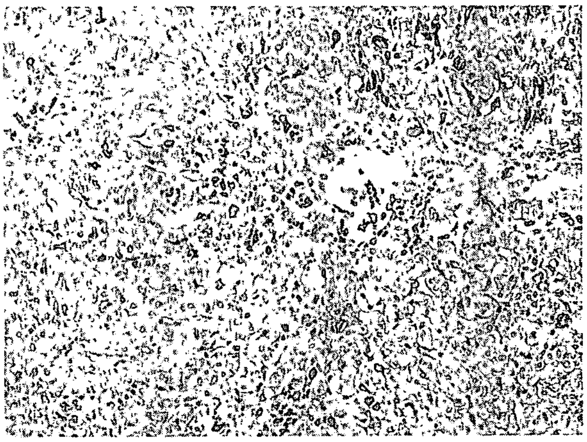

Fig. 1—Bile thrombi are seen in bile canaliculi in the central portion of the liver lobule in the vicinity of a dilated central vein (Hall's stain for bilirubin, original magnification x250).

diagnoses were cholestatic jaundice and transient proximal renal tubular acidosis.

The mother's postpartum course was complicated by heavy bleeding from the episiotomy site and an elevated prothrombin time which required transfusion of 14 units of packed red cells, 11 units of fresh frozen plasma and 8 units of cryoprecipitate. Subsequently the episiotomy was reopened and an arterial pumper was ligated. She was discharged on the seventh postpartum day with a total bilirubin of 10.6 mg.% and alkaline phosphatase of 485 I.U. Five weeks after delivery her bilirubin was 2.4 mg.% and alkaline phosphatase was 350. By the eighth week postpartum she was anicteric with a total bilirubin of 1.2 mg.% and had a normal size liver clinically. Followed two years later, the patient has had no more episodes of right upper quadrant abdominal pain or jaundice and a subsequent gallbladder x-ray was normal. (Table I).

Comment

The clinical picture of intrahepatic cholestasis of pregnancy, as illustrated by this patient, is fairly distinct. Pruritus appears first and tends to be the most disturbing symptom for the patient throughout the clinical course. The term *pruritus gravidarum* is used to describe the syndrome in those patients who do not become jaundiced and this is felt to represent a *forme fruste* of the full blown syndrome. Icterus usually appears within ten days of the pruritus, with its mean onset at about the 26th week of pregnancy,[2] although documented cases beginning as early as the seventh week or as late as the 39th week have been reported. Classically the jaundice tends to be mild with bilirubin levels remaining below 5 mg.%. In a review of the world's literature, Haemmerli and Wyss found the highest recorded serum bilirubin level to be 8.4 mg.%.[2] We believe, therefore, that the bilirubin levels in our patient, which peaked at 35.5 mg.% are the highest which have been documented in this disorder to date. The exception was a patient with known cholestasis of pregnancy who was given oral contraceptives. Similarly high bilirubin levels were reported which showed a sustained fall over a four-week period when the drug was discontinued.[6] The alkaline phosphatase levels were never higher than 280 in that case. The importance of our case for the clinician is the realization that bilirubin levels well above 5 mg.% may occur in cholestatic jaundice of pregnancy and that they should not exclude the syndrome from diagnostic consideration. Indeed, the unusually high level of

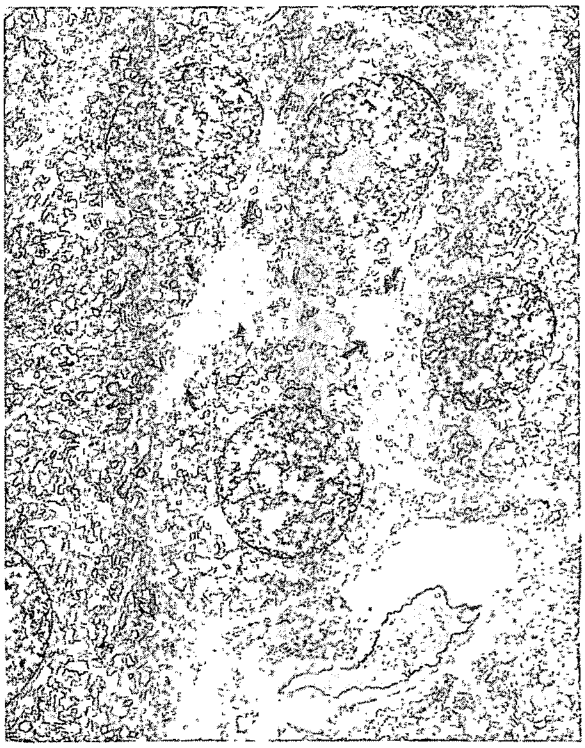

Fig. 2—Three dilated bile canaliculi are seen between liver cells (straight arrows). One of them appears markedly dilated. Some hepatocytes show peribiliary dense bodies. Also seen in one of them are elongated and enlarged mitochondria (curved arrots) (EM, original magnification x6,800).

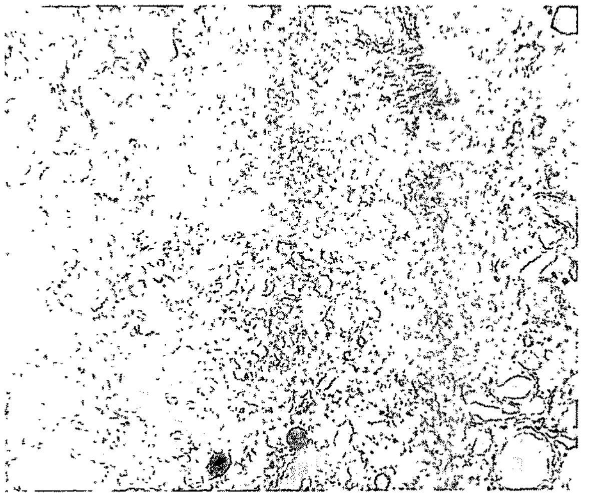

Fig. 3—Higher magnification of dilated bile canaliculus shows loss of microvilli. Membraneous and granular biliary material fills the lumen (EM, original magnification, x38,500).

bilirubin in our patient along with the severe right upper quadrant pain and recurrent short-term fluctuations in bilirubin levels led us away from the diagnosis of cholestasis of pregnancy and towards the probability of extrahepatic biliary obstruction or cholestatic viral hepatitis.

In addition the unusually long duration of the abnormal liver chemistries makes our case unusual and instructive. In their review, Haemmerli and Wyss report that after delivery, serum bilirubin and alkaline phosphatase levels fall rapidly to normal[2] with only exceptional cases requiring as long as four weeks for complete improvement. This patient still had high bilirubin and alkaline phosphatase levels five weeks postpartum and required eight weeks for full recovery of her liver chemistries even though the multiple blood transfusions she received may have favorably altered the exact course of the disease. Although she was clinically well during that period, her slow biochemical recovery was presumably related to the very high bilirubin levels she developed during pregnancy.

It should also be stressed that, contrary to initial claims that the disorder is entirely benign[7] and causes no ill effects on the mother or child, more recent reports rightly contend that cholestasis of pregnancy is associated with shortened gestation,[2, 4, 8, 9] low birth weights,[8, 10] a high incidence of fetal hypoxia[8, 10] and an unexpectedly high incidence of gallbladder disease in the mother.[11] The incidence of meconium-stained amniotic fluid was significantly (i.e. 88%) increased in these infants[12] especially in moderate to severe cholestasis. Since the elevation of maternal bile acids is also present in the fetal compartment,[13] bile acids may be responsible for stimulating fetal colonic motility and meconium passage. In animal experiments, bile acids have been shown to stimulate colonic motility.[14] Haemmerli[15] reported two neonatal deaths in 23 premature births and six still births in 20 infants born after the 36th week of gestation in patients with cholestasis of pregnancy. The deaths were due to intrapartum asphyxia and respiratory distress syndrome and induction of labor or caesarean section may be justified in selected cases.[16, 17] Other reports[16–19] note birth weights of less than 2.500 gm. in 30% of these cases with a prematurity rate of 29-33%. It has been proposed that in pregnancies complicated by maternal cholestasis, the fetal liver has a reduced capacity to change 16-α hydroxylate dehydroepiandosterone (DHES) into estriol precursors. Increased amounts of DHES may thus reach the placenta and be metabolized through an alternative steroid pathway to estradiol, the active hormone. Recently an estradiol surge has been implicated in premature delivery.[20, 21] As illustrated by our patient's child, fetal bile acid levels have recently been shown to be elevated in this disorder[22] with mean levels of 5.6 ng./ml. reported as compared to normals of 1.8 ng./ml. In addition, severe maternal hyperbilirubinemia often results in cord blood levels of unconjugated bilirubin similar to the mother's and may require exchange transfusion for the newborn. In experimental animals there is evidence for transfer of unconjugated bilirubin across the placenta in both directions. In humans there is no evidence to support or refute the possibility that bilirubin diffuses across the placenta[23] but such diffusion seems likely as the cause of the indirect hyperbilirubinemia seen in our case.

The recent literature emphasizes the less than benign nature of the syndrome as related to more pronounced emesis and the increased predisposition to gallstones seen in this disorder. In a study of 57 patients with this entity, Johnson, et al[24] noted that vomiting was more frequent and prolonged in these patients as compared to controls. Food and drug idiosyncracies to penicillin, sulfonamides, strawberries, fish and oranges were also found more commonly in these cases.

There appears to be a significantly higher incidence of gallstones in patients with cholestasis of pregnancy. A recent report[24] noted a 16% incidence of gallbladder disease in a series of 57 patients which was significantly higher ($P < 0.05$) than the 7% incidence found in controls, although it was not specified what the gallbladder disease entailed. Similarly, Samsioe, et al[25] in 1975 reported a higher incidence, compared to controls, of radiographically documented biliary disease developing after delivery in patients with cholestasis of pregnancy. Investigations into this predisposition to gallbladder disease in patients with cholestasis have produced interesting findings about alterations in their bile acid pools and lipid metabolism.

Comparisons of gallbladder bile, obtained at caesarean section, between normal pregnant females and cholestasis of pregnancy showed marked changes in bile acid composition.[25] In normal pregnancy, the ratio of cholic to chenodeoxycholic acid is approximately 3.6:1. In pregnant patients with cholestasis,[26] this ratio was found to be 9:1. Nonsulfated deoxycholic acid, normally present in the bile of healthy pregnant females was not detected in the bile of patients with cholestasis.

Furthermore, an abnormal serum lipoprotein, lipoprotein X, has been found in almost all patients with cholestasis of pregnancy.[24, 27] Lipoprotein X migrates electrophoretically with the β-lipoproteins and in a recent report[27] was found to be a good index of liver dysfunction in cholestasis of pregnancy, since lipoprotein X levels correlated well with the concomitant values of bilirubin, alkaline phosphatase and transaminases. Increased cholesterol, phospholipids, triglycerides, pre-β-lipoproteins and low density lipoproteins and decreased high density lipoproteins are also found in cholestasis of pregnancy when compared to pregnant controls. These changes, however, are not present in the *pruritus gravidarum* stage.[27] The fatty acid composition of serum lecithin has also been shown to be abnormal in patients with cholestasis of pregnancy.[28-30] Lecithin, the major phosphatide in serum, is synthesized in the liver by one of two pathways. The faster and quantitatively dominating cytidine-diphosphate choline diglyceride pathway (Pathway I or Kennedy pathway) is stimulated by bile acids and causes the appearance of lecithin with palmitic acid (16:0) in the 1-position and oleic (18:1) or linoleic acid (18:2) in the 2-position. Pathway II (Greenberg pathway) with methylation of phosphatidyl-ethanolamine preferentially causes the production of lecithin with stearic acid (18:0) in the 1-position and arachidonic acid (20:4) in the 2-position and is enhanced by estrogens. In normal pregnancy, serum lecithin composition is characterized by high levels of palmitic and oleic acid with stearic and arachidonic acids being low.[30] Thus normal pregnancy is in a sense "cholestatic" with Pathway I the predominant source of lecithin. Recently,[29] in an analysis of lecithin in patients with cholestasis of pregnancy, it was noted that early in the course of the disorder (less than two weeks' duration) palmitic and linoleic acids are low while arachidonic acid is high, while late in the course (more than two weeks) oleic acid levels rise, palmitic acid is even lower and the ratio of linoleic to arachidonic acid is reversed. It appears then that the initial stages of cholestasis of pregnancy are characterized by an "estrogenic" fatty acid pattern in serum lecithin while in longstanding cases a "cholestatic" pattern is observed.[31] Four to eight days after delivery, patients with cholestasis were found to have lower levels of archidonic acid, as compared to controls, presumably as a result of the continued effect of cholestasis on Pathway I.[30] Finally, in a report[32] on 20 women eight to 21 months after a pregnancy complicated by cholestasis, it was reported that compared to normal females, serum lecithin composition in these patients was characterized by lower palmitic and oleic acid content and a higher portion of stearic acid, indicating a shift to the estrogen-enhanced Pathway II. These findings suggest that an increased sensitivity to estrogen exists in this disorder and further support the over all hypotheses of increased liver sensitivity to estrogens as the etiologic factor in cholestasis of pregnancy. In addition, since lecithins have been shown to be of importance in the solubility of cholesterol in bile, altered liver lecithin metabolism in patients with cholestasis of pregnancy along with altered bile acid pools may well be responsible for the formation of lithogenic bile and thus explain the predisposition to gallstones seen in this disorder.

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CLINICAL VIGNETTE

Syphilitic Hepatitis

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Liver involvement in syphilis varies with the stage of the disease. The presence of fibrosis, *gumma* and *hepar lobatum* are well described in patients with late and congenital syphilis.[1] On the other hand since Hahn's review of 1943,[2] only eight cases with secondary syphilis have been described in the literature.[3-11] With the new acceptance of aberrant sexual practice there has been an increase in the prevalence of venereal diseases and emergence of new syndromes related to homosexuality.[12]

This case report illustrates one of the manifestations of syphilis that may be easily confused with other causes of jaundice.

CASE REPORT

M. J. S. is a 27-year old black, male, sanitary worker who noticed a small painless penile ulcer two weeks prior to admission. One week later the ulcer cleared but the patient developed polyarthralgias, skin eruption, anorexia, nausea and mild right upper quadrant discomfort. On admission, he had a temperature of 38° C, with a generalized maculopapular rash, right knee effusion and a tender liver with a span of 16 cm. by percussion. There was no evidence of splenomegaly, lymphadenopathy, edema, ascites, or other stigmas of chronic liver disease. His laboratory studies revealed a hematocrit of 41%, hemoglobin of 12 gm.% and white blood cell count of 6,300 with a normal differential. Urinalysis was normal except for the presence of 10-15 white blood cells per high power field. His RPR and FTA were both positive with a sedimentation rate of 50 mm./hr. The heterophil aggulutination test, antinuclear antibody, *L.E.* phenomenon, rheumatoid factor and HBsAg were negative. Cultures of blood, urine and right knee synovial fluid were negative. His prothrombin time was normal and the liver tests are summarized in Table I.

The diagnosis of secondary syphilis was made and the patient was started on penicillin therapy on the second hospital day with a complete resolution of his clinical illness in four days. The markedly elevated SGOT and alkaline phosphatase improved rapidly after the institution of therapy. A liver and synovial membrane biopsy were performed on the third hospital day. The liver biopsy (Fig. 1) revealed a well preserved hepatic architecture with areas of focal necrosis and portal inflammation. The inflammatory infiltrate was composed predominantly of polymorphonuclear cells. There was no evidence of cholestasis and spirochetes could not be demonstrated on silver stain. The synovial membrane biopsy revealed a nonspecific lymphocytic inflammatory infiltrate.

COMMENT

The diagnosis of syphilitic hepatitis in this case is supported by the history of chancre, the positive RPR and FTA and the prompt response to penicillin therapy.

The morphologic changes on liver biopsy, the negative HBsAg, the rapid improvement in liver tests after penicillin therapy and the lack of history of recent drug ingestion speak strongly against viral hepatitis, obstructive jaundice or drug-induced hepatitis.

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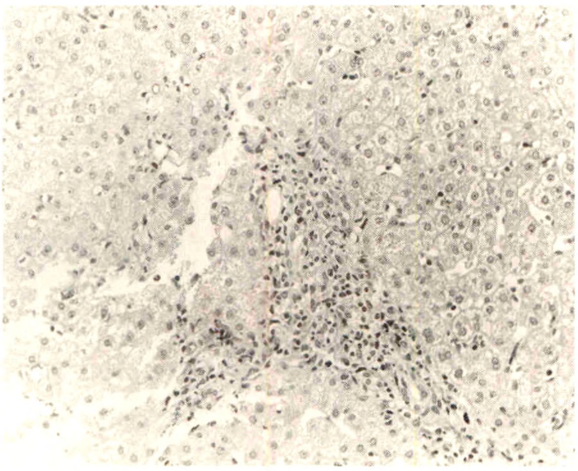

Fig. 1—Percutaneous liver biopsy with mixed inflamatory infiltrate in a portal field (Hematoxylin and eosin, original magnification x400).

Only eight cases of syphilitic hepatitis have been reported in the english literature.[3, 11] Portal inflammation and focal necrosis were present in all patients,[3–11] while three had pericholangitis[4, 5, 7] and one bridging necrosis.[4] Spirochetes were demonstrable in only two patients.[5, 8]

The severity of the histologic changes probably vary with the virulence and duration of spirochetemia. The early institution of therapy in our patient may have prevented the development of cholestasis and vasculitis.

The serum alkaline phosphatase was disproportionately elevated in our patient and in all patients reported in the literature. The presence of such an abnormality in a patient with secondary syphilis should alert the physician to the possibility of syphilitic hepatitis. Appropriate therapy of the primary disease results in prompt resolution of the hepatitis.

TABLE I

LIVER TESTS

Hospital day	SGOT	Alkaline phosphatase	Serum bilirubin
	(N < 45)	(N < 85)	(N < 1.0)
1	400	465	0.6
4	217	440	0.5
10	70	150	0.4

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CLINICAL VIGNETTE

Inflammatory Fibroid Polyp of the Duodenum

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Inflammatory fibroid polyp of the gastrointestinal tract is an unusual lesion of apparent submucosal origin but of unknown etiology. The stomach is most commonly involved with typical presentation being a rounded or oval polyp in the gastric antrum. Occurrence in the duodenum is distinctly rare since only three previous cases have been reported. We present a patient with an unusually long inflammatory fibroid polyp arising in the third portion of the duodenum.

Inflammatory fibroid polyp (IFP) is an uncommon entity of the gastrointestinal tract. The lesion typically presents as a polypoid mass in the gastric antrum but has been found throughout the intestinal tract.[1-5] The duodenum is a rare site of occurrence with only three previously reported cases noted in a recent review.[2] We present a case of an unusually long IFP of the third portion of the duodenum.

CASE REPORT

A 56-year old male presented to North Carolina Baptist Hospital with a 20-year history of presumed peptic ulcer disease treated intermittently with bland diet and antacids. One year prior to admission he noted increasing epigastric pain which was relieved by food and antacids but exacerbated by an empty stomach. Infrequent episodes of melena were also observed during this time. No allergic history was elicited. Physical examination was unremarkable. Pertinent laboratory results included a leucocyte count of 7,600 with 3% eosinophils, a hemoglobin of 12.1 gm.% and a trace of blood in the stool.

An upper gastrointestinal series revealed an elongated mass measuring at least 10 cm. in length in the third portion of the duodenum (Fig. 1). The stomach appeared normal and a concomitant small bowel study failed to show any additional filling defects. Endoscopy performed with the Olympus GIF-D3 panendoscope clearly demonstrated a long finger-like polyp of the distal duodenum. The mucosa at the tip of the lesion was erythematous and eroded. Superficial biopsy revealed chronic inflammatory granulation tissue.

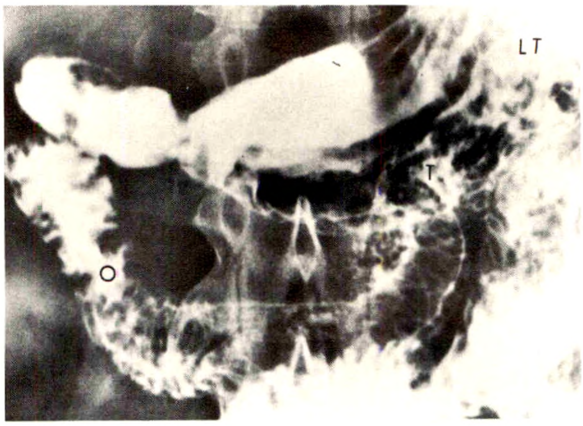

Fig. 1—An elongated filling defect is present in the distal duodenum originating (0) near the inferior duodenal flexure. The tip (T) of the polyp reaches almost to the ligament of Treitz (LT).

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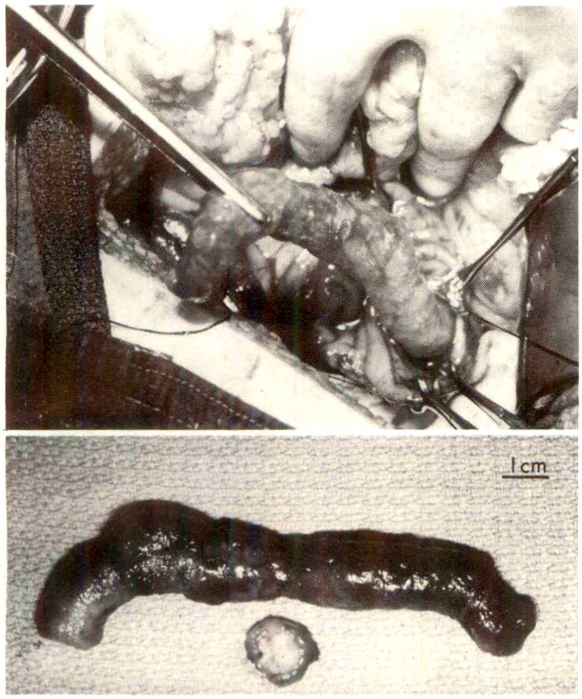

Fig. 2—Operative photograph (top) showing extrusion of the polyp via a duodenotomy. The specimen (bottom) immediately after surgical removal demonstrating its gross morphology.

The patient was taken to surgery and, via a duodenotomy, a 1.5 × 12.5 cm. polyp was removed (Fig. 2). Mucosal erosion was noted at the tip of the lesion. Final pathologic interpretation was inflammatory fibroid polyp (Fig. 3).

COMMENT

Although an uncommon lesion of the gastrointestinal tract, inflammatory fibroid polyp has been variously described. Consequently, a confusing terminology for this lesion exists in the literature and includes such labels as gastric fibroma, inflammatory pseudotumor, eosinophilic granuloma, submucosal granuloma with eosinophilic infiltration and erroneously eosinophilic gastroenteritis.[1-7] Even the term "inflammatory fibroid polyp" is not completely satisfactory since the true etiology has yet to be determined. Presumptive causes for the polypoid growth have implicated neoplastic, inflammatory, neurogenous[8] and allergic origins with most authors favoring an inflammatory pathogenesis. No specific infectious agents have been isolated. Thus, the term "inflammatory fibroid polyp", as first proposed in 1953 by Helwig and Ranier,[1] seems a suitable solution for naming these lesions at present and avoids addition of other terms to an overcrowded nomenclature.

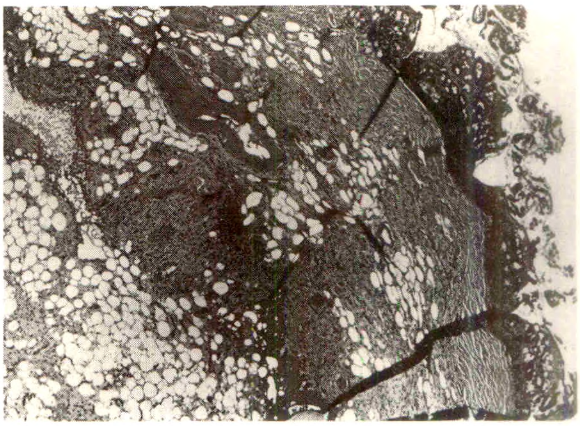

Fig. 3—Photomicrograph revealing a mixed fibrovascular stroma with vessels of varying caliber. Eosinophils were distributed scantly throughout the section. Partial erosion (right) of duodenal mucosa is also evident (Hematoxylin and eosin, original magnification x10).

Approximately two-thirds of these polyps occur in the stomach, most often in the antrum.[2] The duodenum is a rare site for IFP with only three such lesions noted in a recent extensive review.[2] Great diversity in gross morphology has been observed varying from small sessile protuberances through pedunculated polyps to elongated finger-like masses. Ulceration of overlying mucosa is commonly evident. Our case is unusual in being not only the fourth reported lesion arising in the duodenum but also the longest in length (a 9.5 cm. antral polyp being previously described).

Histologically, the lesions appear to arise from the submucosa and are composed of a loose connective tissue stroma. Increased vascularity is present with vessels of differing size and wall thickness. Tissue eosinophilia varies enormously from minimal scattered cells to striking diffuse infiltration. Plasma cells and leucocytes may also be seen but usually in small numbers. True granulomas are rare.

Clinically, a slight male predominance (1.3:1.0) was noted by Johnstone and Morson.[2] The age at presentation ranged from 2-90 years with a mean of 53 years. Abdominal pain was the most common symptom followed by weight loss. Other gastrointestinal signs such as bleeding and anemia were found less frequently. Although symptoms were usually present several weeks to months before patients sought medical attention, duration as long as 10 years or more may be seen. Occasionally, the lesion is found incidentally at operation or autopsy. In contradistinction to eosinophilic enteritis, the peripheral blood smear in those with IFP shows a normal eosinophil count in virtually all patients. Thus, eosinophilic gastroenteritis and inflammatory fibroid polyp are felt to represent two distinctive entities.[2, 6]

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CLINICAL VIGNETTE

Intestinal Strongyloidiasis

A Case Report and Review of the Literature

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A patient infected with *Strongyloides stercoralis* presented with hematemesis and abdominal pain mimicking peptic ulcer disease. Radiologic evaluation, however, suggested Crohn's disease of the proximal small intestine. Aspiration of intestinal fluid and a small bowel biopsy lead to a diagnosis of invasive strongyloidiasis. This case is presented and the literature reviewed to demonstrate the protean manifestation of this parasite which commonly involves the gastrointestinal tract.

Introduction

The clinical importance of strongyloidiasis in this country is becoming apparent. Publications have stressed the high incidence of parasitic infection in troops returning from Vietnam,[1] patients in mental institutions,[2] those on immunosuppressive medication[3, 4] and those emigrating from endemic areas.

The unique life cycle and the capacity for autoinfection of this nematode allows it to live many years in a symbiotic relationship with its host.[5] Although only 50% of those harboring *Strongyloides* are symptomatic, hosts may develop symptoms years after being infected. This may happen spontaneously, because of concurrent illness, or because of treatment with corticosteroids or immunosuppressive drugs.[1, 3, 4] The resulting hyperinfective state has resulted in high morbidity and mortality.

We recently have had the opportunity to investigate a patient with intestinal strongyloidiasis. The case is presented and the literature reviewed to illustrate the protean manifestations of this disease.

Case Report

The patient is a 23-year old male from the Dominican Republic who has been living in New York City for the past six years. After an apparent episode of hematemesis of uncertain cause in 1973, he began having intermittent, postprandial, epigastric pains, occasionally relieved by milk or Alka-seltzer. The day prior to admission he became nauseous and vomited a small amount of bright red blood. He was given Mylanta® with some relief but he then developed melena and diarrhea. Because of persistent weakness and dizziness he came to Columbia-Presbyterian Hospital. An NG aspirate revealed bright red blood. The patient's blood pressure was 120/80; pulse, 108/min. supine changing to 100/70 and 120/min. respectively upon standing. The rest of the physical examination was normal except for mild epigastric tenderness. A CBC showed a normocytic anemia of 28% with a WBC of 6,900 containing 6% eosinophils. All bleeding/clotting parameters were normal as were all routine laboratory profiles except for a cholesterol of 112

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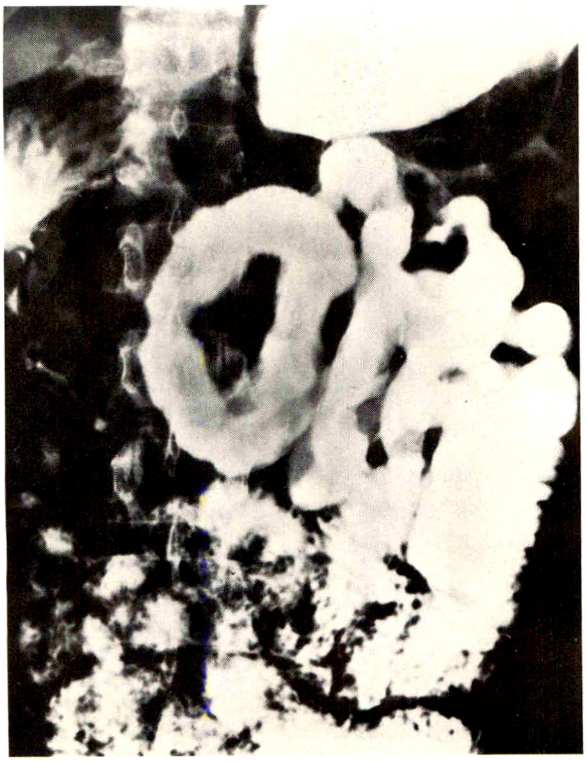

Fig. 1—A dramatic difference is noted between the featureless, stenotic loops of the proximal jejunum and the normal plical pattern of the rest of the small bowel.

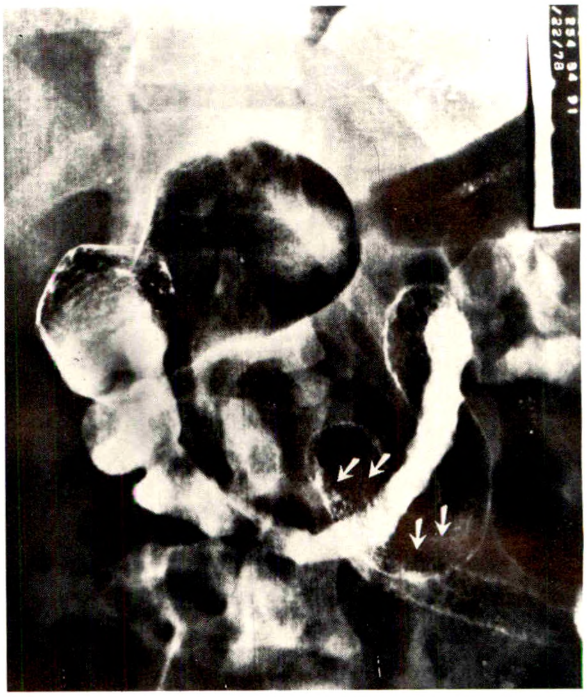

Fig. 2—Air contrast relief of the portion of the jejunum shows a reticular network of thin collections of contrast (arrows). The long axis of these collections runs parallel to the long axis of the jejunum and these represent myriad linear ulcers which may be in part responsible for the patient's hematemesis.

mg.% and a total serum protein of 4.5 mg.% with a serum albumin content of 2.9%.

Vital signs stabilized with the administration of intravenous fluids and two units of packed red blood cells. Although endoscopy revealed brisk bleeding in the duodenal bulb, no ulcer crater could be visualized. The patient was treated for duodenal ulcer disease with cimetidine and hourly antacids and he improved clinically. An upper gastrointestinal series failed to reveal an ulcer in the duodenal bulb. Instead it showed the entire duodenum and first five to six loops of the jejunum to be narrowed and almost featureless with absence of the normal mucosal pattern (Fig. 1). Some tone was present in the muscular coat of the wall, however, with loops appearing narrower on some films than on others. No large ulcers were noted but a network of discreet, fine horizontal and vertical fissures were seen in one loop of proximal jejunum (Fig. 2). No active segmentation or peritstalsis was found in the involved segments. The rest of the small bowel, including the terminal ileum, was completely normal. The colon was not studied. Sigmoidoscopy to 25 cm. was normal.

Because of a persistent eosinophilia and the unusual radiographic findings, the patient underwent repeat endoscopy, Crosby capsule small bowel biopsy and a duodenal fluid aspirate. An ulcer was still not demonstrated, although the duodenal bulb was markedly deformed. There was, however, marked friability of the distal antrum and duodenum with a diffuse, whitish exudate present on the duodenal mucosa. Both the duodenal aspirate and small bowel biopsy (Fig. 3) revealed typical larvae of *Strongyloides stercoralis*. There was no evidence of Crohn's disease or lymphoma present. Stool examinations were also positive for the larvae of *Strongyloides*. The patient was treated with 25 mg./kg. of thiobendazole (p.o. b.i.d. for three days) and discharged symptom-free. A third endoscopy one week later revealed less friability of the mucosal surface but the whitish duodenal exudate persisted. At this time repeat duodenal aspi-

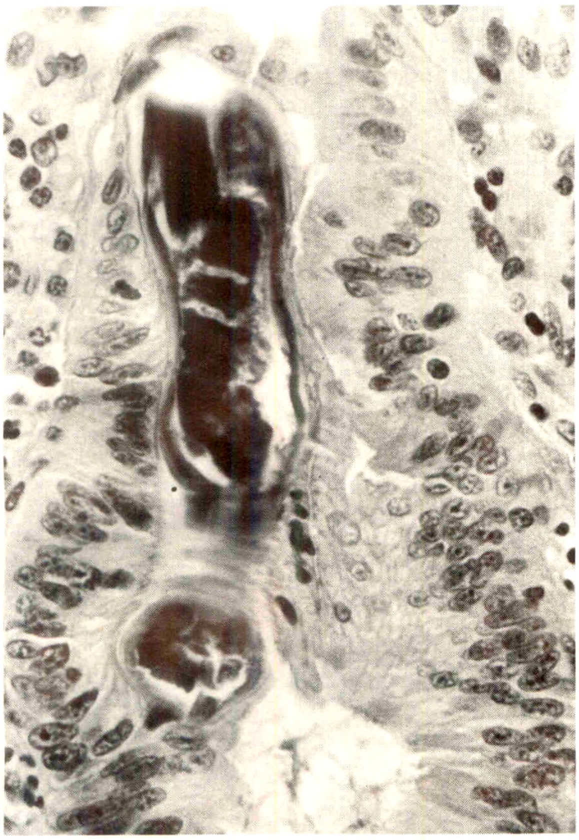

Fig. 3—Small bowel biopsy demonstrates adult female worm located within the jejunal mucosa with minimal inflammation (Hematoxylin and eosin stain, original magnification x1,000).

rates and biopsies were negative for adult or larval forms.

LIFE CYCLE

Strongyloides stercoralis can exist in the soil as free living adult worms or can parasitize man by becoming filariform (infective) larvae which penetrate the skin and cause cutaneous larval migrans similar to hookworm. It is then carried to the lungs through the venous system where it reaches "adolescence" and can be coughed up into the pharynx and enter the gastrointestinal tract but preferentially the proximal small intestine. Here the female adult worm burrows into the mucosa and then lays eggs, which hatch to form rhabitiform larvae. These can be excreted in the feces or become filariform larvae which can then reinvade the ileum or colon (internal autoinfection) or even the perineal area (external autoinfection).[5] In this way the nematode may remain present in the host for years—20-30-year infections are not uncommon.[5]

COMMENT

The clinical presentation of *Strongyloides* infection may be acute or chronic. Although more than 50% of infections are asymptomatic, *Strongyloides* can rarely cause severe acute symptoms when it undergoes a hyperinfective state. This appears to be more common in debilitated,[6, 7] or immunosuppressed patients,[1–4] whereas by an unknown mechanism, presumed to be related to decreased host defense mechanisms, there is a marked increase in autoinfection. This phenomenon is associated with a high morbidity and mortality usually secondary to shock, sepsis and pneumonia[6] with larvae being described in literally every organ of the body including granulomatous hepatic injury.[8]

The more common presentation is that of chronic infection and symptoms are often referable to the gastrointestinal tract. Manifestations of infection include nausea, vomiting, anorexia, diarrhea, weight loss and most commonly mid epigastric pain often related to meals, which can commonly mimic peptic ulcer disease.[9] Hematemesis is rare[6] but occult gastrointestinal bleeding is common especially in severe disease. This may be secondary to ulcerated mucosa or disseminated intravascular coagulopathy.[6, 10] Patients can also rarely present with an acute abdominal crisis[11] including intestinal obstruction.[6] Esophatitis, gastritis and duodenal jejunitis have all been recorded.[6] Protein-losing enteropathy and malabsorption with a picture mimicking tropical sprue has been reported.[12, 13] The patient in the present report did have a low cholesterol, decreased total protein and albumin level suggestive of protein loss and malabsorption. No other tests for malabsorption were performed.

Strongyloidiasis, as previously mentioned, can mimic inflammatory bowel disease.[1] In this regard it should be mentioned that granulomas occurring around larvae in the mucosa may be found and thus cause diagnostic confusion.[6, 14] Indeed in the present case, the radiographic features suggested inflammatory bowel disease involving the duodenum and jejunum. Such a differential diagnosis assumes increasing importance since disseminated strongyloidiasis has been reported to result from immunosuppressive therapy, i.e. Imuran or corticosteroids.

The diagnosis may be suggested by an unexplained peripheral blood eosinophilia. In, however, severe cases or patients already on steroids the eosinophil count may be normal.[6] Skin tests and other blood tests have not been very helpful.[6, 15] Stool specimens will not usually show eggs since the larvae are intermittently passed.[1, 6] The Baermann Stool Filter Technique seems to give an increased yield.[6] While duodenojejunal fluid aspiration has a success rate of approximately 90%,[1] small bowel biopsy success has been poor. Biopsy was successful in our case because of the large number of worms.

Review of the radiologic literature reveals that the majority of cases have been described as having mild to moderate dilatation of the duodenum and first portion of the jejunum. This is accompanied by diffusely thickened "folds" or *valvulae conniventes* in the affected areas, decreased segmentation activity and thus a diminished rate of antegrade peristalsis and a "smudged" mucosal outline.[16-18] The other major presentation is that of a narrow tube with no mucosal pattern. The lumen of the duodenum and jejunum is extremely smooth, the mobility of the bowel is markedly reduced and hence there is a "rigid, pipe stem" appearance.[9, 19] Ulceration has been described in both forms and has taken the form of shallow "serrations" in the contour of the bowel wall.[16, 20] Furthermore, while some have described this narrow, tubular appearance as being irreversible because of fibrosis in the intestinal wall, no documentation of fibrotic replacement has been forthcoming and others have demonstrated a return to a more normal appearing mucosal pattern after antihelminthic therapy.[17, 21] The most reasonable radiographic differential diagnosis consists of Crohn's disease and non-Hodgkin's lymphoma. The long segment involvement is characteristic of both, however, more nodularity and variations of luminal caliber are seen in these two diseases. The other possibility would be either arterial or venous insufficiency resulting in hemorrhage, edema and fibrosis. Ischemia, however, practically never affects the duodenum because of its rich blood supply from multiple sources.

Anyone harboring the nematode should be treated and family members should be investigated. Thiobendazole 25 mg./kg. p.o. b.i.d. × 3 days is the drug of choice with success estimated at 90-100%.[6-13] Some authors suggest a second course three to four weeks later if the initial infection was severe.[6] Hyperinfective states may respond to this oral medicine and should be given this drug. Supportive measures should be performed and appropriate cultures taken. Prior reports have shown no tissue or fluid nematodes within one to two weeks of starting therapy with loss of eosinophilia by eight weeks.[13]

SUMMARY

A case of strongyloidiasis involving the proximal small intestine has been reported with a review of the literature to illustrate the protean manifestations of the parasite which can mimic closely several gastrointestinal disorders both clinically and or radiologically with potentially fatal consequences.

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STATE OF THE ART

Flexible Sigmoidoscopy—Why, Where and When?

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There is no question that flexible fiberoptic sigmoidoscopy provides a significantly higher level of examination and a correspondingly higher yield of pathology when compared to conventional (rigid) sigmoidoscopy.[1-6] There is also no question that sigmoidoscopy is of definite value as a screening technic for polyps and cancers of the rectosigmoid in asymptomatic or symptomatic patients over the age of 40. If this increased level of examination and yield (flexible sigmoidoscopy) can be accomplished with relatively similar increased savings to the patient in time, safety and expense, then flexible sigmoidoscopy may replace rigid sigmoidoscopy in the future.

Fiberoptic sigmoidoscopy is not a new procedure, for fiberoptic sigmoidoscopy was the initial breakthrough in the fiberoptic examination of the colon as reported by Overholt in 1969.[7] The concept of examining the lower one-third of the colon *only* fiberoptically and the concept of a flexible fiberoptic sigmoidoscope, however, are relatively new. The magnification provided by flexible instrumentation provides a larger, clearer and closer view of pathology if the comparison is made by one who is experienced with both types of instrumentation. Papers regarding the application of flexible sigmoidoscopy are appearing in the literature.[2-5] These studies and other cooperative clinical studies are in progress to determine where the concept of flexible fiberoptic sigmoidoscopy fits into the scheme of the diagnosis and treatment of colon diseases.

The recently popularized and rather widely accepted concept that the colorectal adenoma is the most important precursor lesion for large bowel cancer has prompted more extensive interest and effort in the earlier detection of polyps and cancer. Morson, in his preface to his manuscript on "The Pathogenesis of Colon and Rectal Cancer", stated that: "Colorectal cancer is one of the most common forms of malignant disease, which is essentially curable if discovered in its early stages, and in theory preventable if detected in its precancerous phase".[8] Yet, there is no effective screening technic for colon polyps and cancer. Hemoccult® testing of the random stool specimen is effective. Its relatively low but significant yield makes it useful as a yearly test in patients over 40 but it is not effective enough as a mass screening technic. The barium enema examination and total colonoscopy are also excellent and effective methods of evaluating the colon. Neither is practical nor cost effective enough to be used as a screening procedure in asymptomatic patients.

Flexible sigmoidoscopy is the best screening test available currently. Statistics have revealed a noticeable change in the distribution of colon cancers. A lesser number of cancers are within reach of the rigid sigmoidoscope now as compared to the past. In allowing a higher level of examination, flexible sigmoidoscopy therefore improves not only the level of examination but correspondingly increases the yield in pathology so that once again approximately two-thirds of colon cancers are actually within reach of the flexible sigmoidoscope. Flexible sigmoidoscopy, therefore, is not really just an instrument but more importantly it is a concept: The concept being that flexible sigmoidoscopy is currently the best screening technic available to us in a country where colon cancer and polyps are so prevalent.

AN OFFICE PROCEDURE

The preparation (a single phospho-soda enema) is the same for both flexible and rigid sigmoidoscopy. Discomfort or pain to the patient is the same with both methods, provided the procedure is terminated at the first level of minimum discomfort. The flexible instrument and its corresponding Sims position are actually less discomforting to the patient; both methods can be painful if the endoscopist insists on instrumentation to the highest level in *all* patients. Risks or complications are present with either method and do appear to be slightly greater with flexible sigmoidoscopy, especially when performed by individuals not experienced with fiberoptic instrumentation.

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* Edited by Walter Harvey Jacobs, M.D., F.A.C.G.

The duration of sigmoidoscopy is relatively brief by either method, provided the flexible instrumentation is performed by one who is experienced with these technics. In experienced hands, fiberoptic sigmoidoscopy usually takes less than five minutes, whereas rigid sigmoidoscopy usually takes less than two to three minutes. Therefore, if the busy proctologist performs 10-15 sigmoidoscopies during afternoon office hours, flexible sigmoidoscopy may not be practical on a routine basis; perhaps this priority will change. For most gastrointestinal physicians (internists or surgeons) who perform less than five sigmoidoscopies a day, the additional time for flexible instrumentation may not be a deterring factor.

In my opinion, the real value of fiberoptic sigmoidoscopy is in the office setting where a majority of the sigmoidoscopies are performed. Here, with no additional preparation, no premedication, no significant increases in time especially to the patient and no significant increased risk, flexible sigmoidoscopy will undoubtedly be of value since it is acknowledged that there will be an increased level of examination and a corresponding increased yield in pathology. In evaluating an asymptomatic patient over the age of 40, flexible sigmoidoscopy is preferred because of its higher level of instrumentation and yield, especially since this patient will not always be needing a barium enema examination. Symptomatic patients (rectal bleeding, guaiac positive stools or significant change in bowel habits) will generally require a barium enema evaluation to evaluate their symptoms. When the symptomatic patient is being evaluated initially in the office, sigmoidoscopy (either method) would be appropriate and would be expected most probably by the patient at this time. If the symptomatic patient is already hospitalized and is being seen in consultation, the physician can elect to perform sigmoidoscopy before or after the barium enema examination. Once the barium enema has been performed and colon endoscopy is indicated, the choice of instrument (length) is a function of the physician's judgment, experience and the barium enema findings—and is not a function of the length of the instrument to be used. In the hospital setting, usually total colonoscopy is indicated for the symptomatic (rectal bleeding, polypoid or neoplastic disease suspected) patient.

COST

The cost-effectiveness of flexible sigmoidoscopy is not yet known. The instruments are expensive, although time and competition may bring prices down somewhat. Repairs on fiberoptic instruments can also be expensive, although they allegedly will be less with the flexible sigmoidoscope (shorter instrument), especially if used by an experienced endoscopist and especially if instrumentation is discontinued at the first level of difficulty or discomfort. The physician's fee for flexible sigmoidoscopy will undoubtedly be higher than that for rigid sigmoidoscopy. If flexible sigmoidoscopy is to replace rigid sigmoidoscopy on a routine basis in the office setting, the cost to the patient will have to be reasonable. One cannot triple the cost of sigmoidoscopy and then recommend it as a routine office examination.

WHO SHOULD DO FLEXIBLE SIGMOIDOSCOPY?

Although I state that I can reach the cecum colonoscopically in more than 90% of patients, in general, I reach the descending colon in approximately 40-50% of patients in the course of flexible sigmoidoscopy in the office, because of my desire to keep this a brief, safe and comfortable procedure. There is some question as to who should do flexible sigmoidoscopy. Should it be limited to those who are experienced colonoscopists, or should all internists, surgeons and family practitioners be encouraged? There are no data to definitely answer this question at this time. My personal feeling is that flexible fiberoptic instrumentation should be performed only by one who is experienced with this type of instrumentation regardless of whether he is a gastroenterologist, a surgeon, a proctologist, or other practitioner. Flexible endoscopy cannot be performed effectively by one who is untrained, unexperienced, or by one who will be using this instrument occasionally. Already, complications with flexible sigmoidoscopy have been reported[6] and can be anticipated with at least a slightly greater frequency than rigid sigmoidoscopy since instrumentation is to a higher level. The appropriate interpretation of endoscopic findings and a corresponding minimum incidence of complications can only be accomplished if the procedure is performed by one who is properly qualified. I doubt that the flexible sigmoidoscope can be put in the hands of the occasional sigmoidoscopist just as the occasional sigmoidoscopist usually does not engage in biopsy or polypectomy technics. It would appear that those of us who perform five or more sigmoidoscopies per week should seek and obtain training and experience with flexible sigmoidoscopy. Until teaching technics have been developed and disseminated and proved effective for flexible sigmoidoscopy, rigid sigmoidoscopy is still the safe and time-tested procedure which should remain within the armamentarium of the occasional sigmoidoscopist and most primary physicians.

CAUTION

Flexible sigmoidoscopy should not be performed on patients with acute inflammatory bowel disease since direct instrument trauma or even simple air insufflation by fiberoptic instrumentation could cause perforation in a diseased bowel segment. Also, polypectomy should not be performed during the initial fiberoptic sigmoidoscopy which has been prepared with a single phosphosoda enema. Proper evacuation of potentially explosive gases may not have been accomplished with this minimum prep in this closed system. More important, the presence of a rectosigmoid polyp and its associated significant incidence of synchronous polypoid lesions higher up in the colon are indications for a barium enema examination and a *total* colonoscopy prior to the removal of any colon polyps.

CONCLUSION

Flexible sigmoidoscopy appears to be a more effective form of initial sigmoidoscopy in that the level of examination and yield of pathology is significantly higher as compared to rigid sigmoidoscopy, provided the patient is not adversely affected by the preparation, time involved, risk and cost. Its primary advantage appears to be in the office setting where patients are anticipating a sigmoidoscopic examination. Its higher level of examination would be of maximum benefit to asymptomatic patients over the age of 40 in whom a barium enema examination may not be planned. Flexible sigmoidoscopy should be performed by physicians who are performing these procedures regularly, be they surgeons, gastroenterologists, or otherwise. In view of the acceptance of the polyp-cancer sequence and in view of the lethal nature of colon cancer in the United States, flexible sigmoidoscopy should be considered as a screening procedure for asymptomatic patients over the age of 40 on an every three to five-year basis.

This is a personal view of the current State of the Art of flexible fiberoptic sigmoidoscopy and reflects the opening chapter on this subject. Future changes in technology, i.e. instrument length and subsequent experience in this field is awaited before the next chapter can be written regarding the value of flexible fiberoptic sigmoidoscopy in the evaluation and treatment of colon diseases.

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THE ENDOSCOPY CORNER*

Colonic Varices

UNUSUAL CAUSE OF RECTAL BLEEDING

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A 46-year old male with recurrent rectal bleeding is reported. Extensive radiographic studies, upper gastrointestinal endoscopy and sigmoidoscopy failed to demonstrate any pathologic findings. Colonoscopy revealed varices in the rectosigmoid area. This paper reviews the subject of colonic varices.

INTRODUCTION

Varices of the colon are a rare and unexpected cause of massive rectal bleeding. The first reported case was in 1954[1] and since that time there have been fewer than 30 additional cases in the world literature. Since the roentgenographic diagnosis of colonic varices can be misleading, colonoscopy has been shown to be a useful additional procedure in the diagnosis of this unusual entity.[2] This report presents a patient with colonic varices diagnosed at colonoscopy and a brief review of this subject follows.

CASE REPORT

A 46-year old white male was referred for colonoscopy to evaluate the etiology of his recurrent bright red rectal bleeding. The patient had three episodes of bright red blood per rectum in the past six months. Three weeks prior to colonoscopy, the patient had undergone hospitalization and evaluation for rectal bleeding when he presented with the passage of an estimated 1,000 ml. of bright red blood.

At the time of hospitalization, the patient had complained of two weeks of vague abdominal discomfort which had not be relieved with food or antacids. He admitted to drinking approximately 3-4 beers per week. He denied episodes of recurrent abdominal pain or pancreatitis. There was no evidence of chronic liver disease, abdominal tenderness, guarding, rebound, organomegaly, or masses. The nasogastric lavage revealed bile stain hematest negative fluid. His hemoglobin was 9.8 gm. and his hematocrit was 30%. Proctosigmoidoscopy to 15 cm. demonstrated normal mucosa with blood coming from above this area. Radiographic examination of the esophagus, stomach and small intestine was normal. Barium enema examination was also normal. Esophagogastroduodenoscopy was normal.

On the day of colonoscopy, the patient was feeling well without complaints and his physical examination was within normal limits. His hemoglobin was 11.3 gm. and his hematocrit was 34.0%. The patient, who had received adequate preparation as an outpatient, underwent total colonoscopy with the Olympus TCF-Type 2L. Markedly dilated tortuous, bluish veins (Fig. 1) were noted over a 12 cm. segment in the rectosigmoid area. The remainder of the examination to the terminal ileum was normal. Angiography was recommended but the patient refused further evaluation or treatment and for the past two months there has been no subsequent bleeding.

COMMENT

Although the actual bleeding site was not identified, we assumed that the colonic varices were the cause of the lower gastrointestinal bleeding. This assumption was based on the fact that colonic varices have been associated with bleeding in the literature and no other pathology or potential bleeding source was noted on extensive radiographic and endoscopic evaluation. Certainly varices involving esophageal and gastric fundic veins are more common and more widely appreciated. What is surprising is that varices of the colon do not occur more frequently considering the commonplace occurrence of cirrhosis and the abundance of inferior mesenteric collateral veins. Several possible

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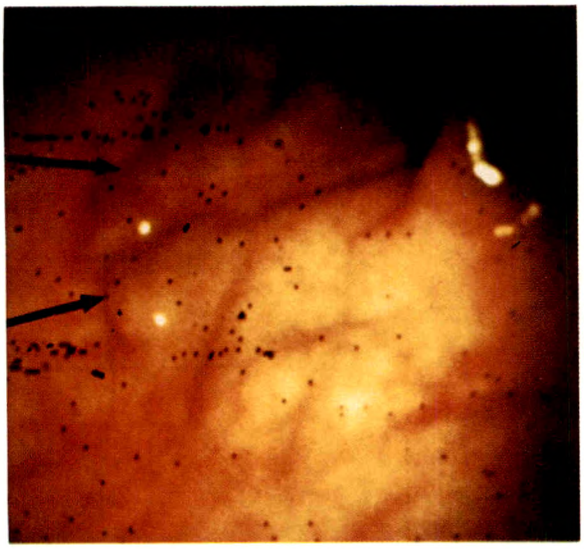

Fig. 1—Endoscopic picture demonstrating dilated tortuous bluish vein (arrows).

causes of colonic varices have been previously considered.[3–5] Levy, et al have suggested that a congenital vascular abnormality could be a necessary underlying factor which becomes more pronounced in the setting of portal hypertension.[6] Other possible predisposing conditions for colonic varices include congestive heart failure with chronic passive congestion, mesenteric vein thrombosis, postoperative intrabdominal adhesions[7] and chronic pancreatitis with splenic vein thrombosis.[8] In some cases (this one included) no apparent associated factor can be discerned.

The majority of published cases of colonic varices presented with rectal bleeding. It is a rare condition with an autopsy incidence estimated to be 1 in 1,500.[3] In half of the cases, the diagnosis was not made or suspected until the time of operation or autopsy. Barium enema is not as useful as would be expected in diagnosing varices of the colon, in part because of the rarity of the condition resulting in a low index of suspicion. The varices can appear as lucent mural filling defects in a linear or cobblestone pattern on barium enema.[9] These defects can be mistaken for carcinoma or artifact.[10] Frequently, however, the barium enema is interpreted as normal; this occurred in nine of 19 previously compiled cases[2] as well as in the present case.

Direct intraluminal visualization of dilated colonic veins is the most reliable way to make the correct diagnosis. Sigmoidoscopy has been repeatedly useful in establishing the diagnosis nonoperatively.[2] Colonoscopy, which has been recently demonstrated to be beneficial in patients with rectal bleeding when the cause cannot be found on barium enema examination or sigmoidoscopy,[11] offers the additional, obvious advantages of excluding other lesions in the colon and viewing varices beyond the reach of the sigmoidoscope. Indeed, varices have been reported in the cecum, ascending and descending colon but are more common in the rectum.[3, 6, 9, 10, 12] The venous phase of mesenteric arteriography can add further useful information with regard to origin and extent of the varices.

Therapy has involved surgical intervention in patients with persistent, massive bleeding. The procedure most often used is either a resection of the involved colon or a decompression shunt in patients with portal hypertension.[13] It is not known whether patients who have bled from colonic varices and then stabilized need surgical therapy.

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THE PEDIATRIC CORNER

Peptic Ulcer in Children

A REVIEW

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INTRODUCTION

Many uncertainties exist regarding the prevalence, etiology, natural history and optimal mode of therapy of peptic ulcer in children. The purpose of this review is to focus on these issues.

Peptic ulcer disease in children has been recognized since 1826, when von Siebold reported a perforated gastric ulcer in a two-day old infant.[1] Until 1941 peptic disease was considered an unusual problem in the pediatric patient. A review at that time made by Bird, Limper and Mayer recorded 119 cases in which surgery had been required. Fifty-three operations were performed for pyloric stenosis, 43 for perforation, 12 for hemorrage and 11 for uncontrollable symptoms. In concluding their review, the authors speculated that a large number of unrecognized and unreported ulcers of a potentially serious nature must exist and urged that more roentgenologic studies be performed.[2] Tudor, 33 years later, reasserted that peptic ulcer was not uncommon in children. Seven hundred ninety-one cases had been reported to the Childhood Registry for Peptic Ulcers and the author quoted a personal experience with 168 cases.[3]

Children with peptic ulcer disease have been divided into two categories: those in whom the ulcer is secondary and occurs within a setting of systemic disease and those with primary peptic disease. Secondary peptic ulceration is associated with such entities as severe burns, i.e. the Curling ulcer, intracranial lesions, i.e. the Cushing ulcer, sepsis, hypoglycemia, shock, acute respiratory disease, leukemia, lymphoma, collagen vascular diseases and immunosuppressive therapy.[4–6] It tends to present as an acute medical emergency with hemorrhage and/or perforation and frequently without pain[5, 7, 8] and appears with equal frequency in the stomach and duodenum regardless of age.[4] Mortality is in part dependent on the nature of the underlying illness but in general tends to be high and in the range of 14-84%.[5, 8–10] Surgery is necessary in the event of perforation, obstruction and uncontrollable hemorrhage. Operative mortality has been variable but in one series was zero.[10] In those who survived after either medical or surgical therapy recurrence of ulcer has been unusual.[5, 7] With the exception of Cushing ulcers, gastric hypersecretion has rarely been observed in acute stress ulcer[11, 12] and thus the simplest operative procedure available such as ligation and plication with drainage has been claimed by some authors to be optimal.[7, 13–15] Others have found superior results with more definitive procedures and prefer vagotomy and pyloroplasty,[10, 13] while others prefer vagotomy and antrectomy in an effort to avoid rebleeding.[16, 17]

EPIDEMIOLOGY

While 80% of ulcers in infancy are secondary, after infancy at least 70% of ulcers are primary.[4, 5] The true frequency of primary childhood peptic ulcers seems unclear. Sultz, et al, reported that the three-year incidence in Erie County, NY increased from 0.5 per 100,000 in the period 1947-1949 to 3.9 per 100,000 in 1956-1958.[18] Miranti reported 68 peptic ulcers in adolescents and young adults diagnosed radiologically during the five-year period 1964-1968 at a large university center.[19] The enrollment averaged 21,576 during the period of the study and represented an incidence of 67 per 100,000. In another report 123 cases of childhood ulcer were reported from a large private pediatric

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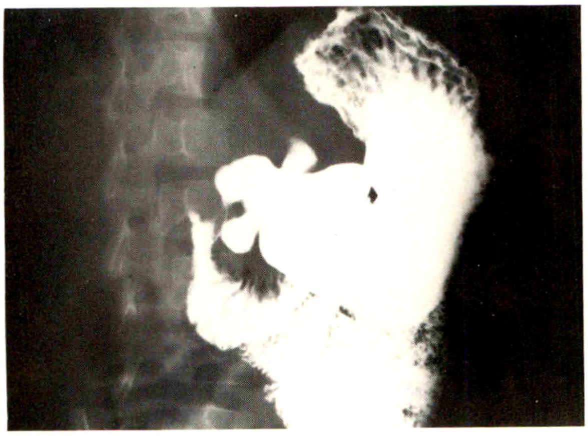

Fig. 1—Clover leaf bulbar deformity and postbulbar narrowing in a seven-year old girl with juvenile rheumatoid arthritis and gastric hyperacidity. Follow-up showed recurrent pain and vomiting.

practice of over 7,000.[20] All cases were documented radiologically and indicated a prevalence of 1.7%. This is surprisingly similar to the prevalence of 1.9% of peptic ulcer in women between ages 15-64.[21] No other studies, however, have reported a similar prevalence.

Tudor reported a predominance of duodenal ulcer over gastric ulcer in childhood, with a ratio of 6:1 and a male to female ratio of 1.3:1.0.[3] The report cited 791 cases.

Prouty also reported a predominance of duodenal ulcer, in which of 337 radiologically verified ulcers in children all but six were duodenal.[22] Williams and Ahmed, however, reported a ratio of only 2.5:1.[23] It is known that in younger children a primary ulcer is generally less common, but is frequently gastric. Deckelbaum, et al, reported 48 primary ulcers of which six occurred below the age of six and all were gastric.

Studies on the epidemiology of childhood ulcer have also noted a common family history of peptic disease. Tudor reports a 20% positive history[3] and Deckelbaum noted a similar finding in primary duodenal ulcer but a negative family history in all cases of primary gastric ulcer.[5]

ETIOLOGY

Genetic considerations seem to play a role in the epidemiology of childhood ulcer, as children with duodenal ulcer, just as adults, show a significant excess of blood group O.[24] Studies of twins have shown a concordance rate of 50% in monozygous twins and only 14% for dizygotic twins.[25]

Psychologic studies on children with duodenal ulcer have shown differences in controls. In one report it was noted that children with duodenal ulcer showed less satisfactory social interactions and both sibling and parental relationships were considered poor.[26] It had also been noted that these children were usually of high intelligence, were over achievers, handled feelings of anger and frustration with difficulty, were inclined to internalize their aggressive feelings and were more docile and submissive than controls. Taboroff, et al, noted other personality characteristics in children with peptic ulcer disease: passiveness covering unexpressed hostility toward parents, overdependence on the mother, fear of loss of a figure upon whom the child was dependent and social withdrawal based on feelings of inadequacy.[27]

The role of gastric hyperacidity has also been assessed in childhood peptic ulcer. Few studies have been performed. It appears, however, that children with duodenal ulcer, like adults, tend to show greater gastric acid secretion compared to controls. Kopel and Barbero reported on gastric acid secretion in infants and children by means of an augmented histamine test.[28] Only normal children were studied and mean basal acid output and maximal acid output were recorded in four age groups. Values determined respectively were .34-.45 mEq./10 kg./hr. and 2.39-2.62 mEq./10 kg./hr. Acidity expressed per body weight increased directly with increasing age. Using the same technic Ghai, et al, studied acid secretion in children with duodenal ulcer and controls.[29] No significant difference in mean basal secretion was noted but controls showed a mean maximal secretion of 2.02 mEq./10 kg./hr. and ulcer patients 3.0 mEq./10 kg./hr. It was noted that children with active duodenal ulcer showed greater acid secretion than those with inactive disease. Nineteen children with duodenal ulcer showed greater acid secretion than those with inactive disease. Nineteen children with duodenal ulcer were studied by Habbich, et al and determined to have a mean maximal secretion of 3.30 mEq./10 kg./hr.[24] The authors concluded that make a firm conclusion due to an inadequate control population. Christie and Ament studied gastric acid secretion in 12 children with duodenal ulcer and in 14 controls.[30] Diagnosis of ulcer was based

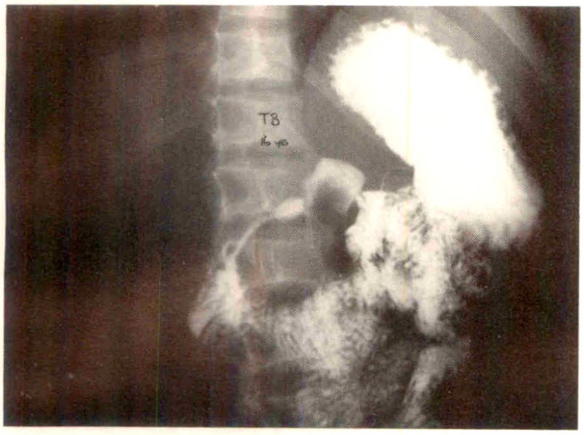

Fig. 2—Postbulbar crater with distal narrowing in a 16-year old boy with symptoms of ulcer disease since age 13. Follow-up showed healing of ulcer followed by recurrence of crater after seven months.

on endoscopic evaluation or presence of ulcer crater on radiologic analysis. Children with active ulcer showed a significantly greater mean MAO and PAO than controls. Results expressed as mEq./10 kg./hr. were respectively 4.86, 5.07 and 2.48, 3.32. Basal acid excretion was greater in children with ulcer but was not significant.

High basal acid secretion has been noted in children with ulcer disease related to the Zollinger-Ellison syndrome. The subject was reviewed by Rosenlund,[31] in 1967 and again by Buchta and Kaplan[32] in 1971 by which time 19 cases, between six and 17 years of age, had been described. These early cases were characterized by a high incidence of penetration, perforation, bleeding, multiple ulcerations, ulceration in atypical locations and multiple surgical procedures prior to eventual diagnoses. In 11 cases reviewed by Rosenlund, none involved islet cell tumors of other endocrine glands, three involved nonbeta islet cell tumor or the pancreas with metastases, two showed islet cell hyperplasia, five showed tumor metastases to liver or lymph nodes only and in one patient no tumor could be found. Seven patients had total gastrectomy and all were alive; of four patients with subtotal gastrectomy three had died.

In a recent publication Regan and Malagelada noted that experience with Zollinger-Ellison syndrome in adults at the Mayo clinic since 1970 showed that half of the patients presented with clinical, roentgenographic and endoscopic findings undistinguishable from these of idiopathic duodenal ulcer or erosive duodenitis.[33] No patients had ulcers in atypical locations (esophagus, distal duodenum, or jejunum) and some patients did not have a distinct ulcer crater but merely superficial mucosal erosive duodenitis. The authors advocated routine use of serum gastrin radioimmunoassay and gastric analysis. Universal employment of such diagnostic procedures would probably markedly augment the diagnosis of Zollinger-Ellison syndrome in children with peptic disease and is clearly indicated.

The symptoms of primary peptic ulcer disease in children vary considerably with the age of the patient.[2, 4–6] Neonates reportedly born without stress may present with perforation, bleeding or both. At surgery or autopsy little cellular reaction, fibrosis, or other effort to localize the perforation has been noted.[2, 6] In older infants poor feeding, vomiting and growth failure may herald perforation or hemorrhage.[6] In children below seven, vomiting is frequent and pain, when noted, is atypical and poorly localized.[4, 5] Bleeding in this age group has been reported to be more frequent than pain, occurring in 33% of these children.[5] In older children pain is the most common symptom of peptic ulcer but is more usually atypical than typical.[5] Bleeding is seen in 50% of older children. In adolescence pain may be similar to that of adult patients with peptic ulcer disease[34] and is usually epigastric or periumbilical.

DIAGNOSIS

Diagnosis of peptic ulcer disease in children has largely been dependent on surgical and pathological findings as well as on radiologic investigation (Figs. 1, 2 and 3). The limitations inherent in a radiologic study had been reported by Goldberg[35] in 1957. It was noted that the average duration of symptoms extended 23 months in children with definitive crater, seven months in patients with bulbar deformity and four months in children with bulbar irritability.

Deckelbaum, et al, reported that in 25% of cases of primary ulcer a repeat barium meal was necessary to establish the diagnosis.[5] Tedesco, et al reported on the utilization of upper gastrointestinal endoscopy in children.[36] Endoscopy was performed safely and without general anesthesia on 50 children and included 17 children with peptic ulcer disease. Radiologic diagnosis of ulcer was obtained

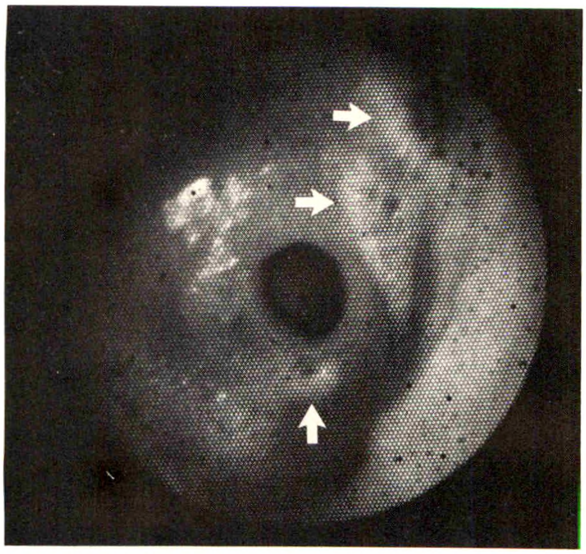

Fig. 3—Kissing antral ulcers in a 13-year old boy with a three-day history of pain and vomiting. Follow-up showed complete healing and no recurrence.

in 47% of cases and endoscopic diagnosis in 88%. Cox and Ament employed conventional gastrointestinal radiography, endoscopy and arteriography in assessing 68 children and adolescents with upper gastrointestinal bleeding and found endoscopy to be the most reliable method of determining the bleeding site.[37] Duodenal ulcer and gastric ulcer were determined to be the most common origins of bleeding. It becomes apparent that when available, endoscopy should be the first diagnostic approach in a child with upper gastrointestinal hemorrhage. This has proven safe even in an infant less than 24 hours old.[38] Endoscopy is also indicated when signs and symptoms are suggestive of peptic disease but radiography is normal or equivocal. It is likely that as endoscopy becomes more available, pediatric radiologists will feel less of a need to make a definitive "call" in less clear cases. Endoscopy, however, should be viewed as a complementary study to radiography and not a replacement of it.

The differential diagnosis of peptic ulcer disease in children includes those entities which frequently must be considered in older patients: functional pain, esophagitis, Crohn's disease, pancreatitis and biliary disease. Other entities generally more specific to the child must be entertained and include: gastroenteritis, appendicitis, Meckel's diverticulum, intussusception, volvulus, heavy metal toxicity (lead, iron, arsenic), testicular torsion and Henoch-Schonlein purpura. It should be remembered that pneumonia, pyelonephritis and diabetes frequently occur with abdominal pain and vomiting in children. When considered, each of these entities can be evaluated by appropriate clinical and laboratory testing.

MANAGEMENT

The medical treatment of peptic ulcer disease in children has largely been based on experience with adults. No placebo controlled studies have been performed in children. Antacid therapy has been the mainstay of therapy and at times anticholinergics have been advocated. No studies have been performed indicating superiority of one regimen of treatment over another. Cimetidine, now in widespread use in adult patients with peptic ulcer, has not been reported on in children with peptic ulcer. At the Buffalo Children's Hospital a limited experience with the use of cimetidine in children with peptic ulcer has not disclosed any complications of therapy and symptomatic improvement has been obtained.[39]

Surgical experience in children with peptic ulcer disease continues to grow as the disease becomes more easily recognized and complications develop. Surgery is indicated in perforation, obstruction, uncontrollable hemorrhage and intractability. Tudor, in 1972, reported that 7.5% of the patients reported to the Childhood Peptic Ulcer Registry had surgery performed and that a review of the world literature yielded a total of 519 cases which were treated surgically.[40] Prouty, however, reported that no surgery was necessary in 337 cases of peptic ulcer,[22] although this series was unusually free of complications. Vagotomy and drainage coupled with ligation of a bleeding vessel or plication of a perforation has been recommended by various authors as the procedure of choice in treating chronic ulcers in childhood.[7, 13, 41, 42] Boley, et al used a puppy model to show that vagotomy and pylorplasty does not affect subsequent growth and development, whereas antrectomy or subtotal gastrectomy did.[43] Seagram, et al reported no recurrence of ulcer using vagotomy and pyloroplasty[13] and Barber, et al reported no recurrence after gastric resection or posterior gastroenterostomy.[44]

Various reports concerning children have noted a 50-70% rate of recurrence or persistence of symptoms of duodenal ulcer if treated medically.[5, 24, 44] Another report, however, based on the experience of the surgical service of a large children's hospital noted that greater than 75% of patients responded to medical management when followed for up to 22 years.[7]

SUMMARY

In summary, the prevalence of peptic ulcer diseases in children remains controversial, however, it appears to be a significant cause of morbidity and mortality. Peptic ulcer may be related to systemic disease, may occur as a primary event, or may be associated with the Zollinger-Ellison syndrome. The nature of the symptoms is age dependent. Analysis of serum gastrin is indicated in peptic disease of children and gastric acidity secretory studies may help define those children likely to suffer duodenal ulceration. Diagnosis is best accomplished by a high index of suspicion coupled with radiologic and endoscopic investigations. Therapy is essentially aimed at reduction in gastric acidity and may be accomplished with the use of conventional antacids. Limited use of cimetidine has produced no untoward effects. Surgery is necessary in cases of uncontrollable hemorrhage, perforation, obstruction and Zollinger-Ellison syndrome. When symptoms are intractable, surgery is also indicated and should be preceded by assay of serum gastrin. A subgroup of children with duodenal ulcer, possibly associated with gastric hyperacidity, seems destined to require long-term medical therapy and in selected cases may benefit from earlier, elective surgery. Prospective studies are needed to more clearly determine the prevalence of peptic disease in childhood, to define prognostic markers for chronicity and complication and to determine optimal modes of therapy.

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THE RADIOLOGY CORNER*

Adenomyomatosis of the Gallbladder

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and

ANN M. LEWICKI, M.D.
Washington, DC

In 1960, Jutras described a group of degenerative gallbladder diseases which he collectively called the *hyperplastic cholecystoses.*[1] Of the cholecystoses, adenomyomatosis and cholesterosis are the most common entities encountered radiographically.[1, 2] Prospective studies have shown that there is present a 5% incidence of hyperplastic cholecystoses on oral cholecystography.[3] It is the purpose of this report to review the radiographic features of adenomyomatosis and so that these can be understood, a brief description of the pathological changes will also be given.

PATHOLOGICAL FEATURES

Adenomyomatosis is a degenerative disease characterized primarily by hyperplasia of the gallbladder wall. The hyperplastic cells retain their structural organization, thus, there is no increased incidence or predisposition toward malignancy. On microscopic examination of the gallbladder wall, the following changes will be seen: 1. The epithelium has proliferated, forming mucosal outpouchings or diverticula. These diverticula may extend into the *muscularis*. 2. The muscular layers of the gallbladder wall are hypertrophied, causing thickening of the wall. On sectioning of the gallbladder wall at oblique angles, the mucosal invagination may resemble dilated glands or cysts. This has given rise to the names "*cholecystitis glandularis proliferans*" or "cystic cholecystitis". It must be emphasized, however, that these do not represent true glands or cysts but merely the involuted epithelium, sectioned so that their communication to the lumen is not demonstrated. These diverticula were first described by Rokitansky in 1842 and later by Aschoff in 1905. Today they are frequently called the Rokitansky-Aschoff sinuses.

Involvement of a gallbladder with adenomyomatosis may be diffuse, segmental or localized. In the diffuse type, there is involvement extending from the cystic duct to the fundus of the gallbladder. With segmental involvement, there may be a normal wall proximal and distal to the lesion. Segmental adenomyomatosis may involve the proximal, middle or distal third of the gallbladder in a localized, circular fashion. In the localized form of adenomyomatosis, a soft, pliable mass may be palpated in the involved area. For such a lesion, the term adenomyoma has been applied. This actually is a misnomer, since it is only a localized area of hyperplasia and hypertrophy which is sharply demarcated from the surrounding normal wall but not limited by a capsule, thus, not a true neoplasm. There is no hyperplasia of actual glands present.

RADIOGRAPHIC FEATURES

Adenomyomatosis is frequently associated with a hyperfunctioning state characterized by hyperconcentration, hypercontractility and hyperexictability on contrast radiography. The hyperconcentration leads to a greater than average opacification of the gallbladder lumen. This occurs because an increased mucosal surface is present. Hypercontractility leads to a more complete emptying of the gallbladder after a fatty meal. This is caused by the muscular hypertrophy of the gallbladder wall. Hyperexcitability is manifested by rapid emptying (usually within five minutes) after a fatty meal. This is due to an abnormal proliferation of nerve fibers in the gallbladder wall. It should be noted, however, that not all of the hyperfunctioning states may be present in an individual case.

The hallmark of radiographic diagnosis is filling of intramural diverticula with contrast material (Figs. 1a and 1b). On oral cholecystography these are demonstrated as small contrast collections that

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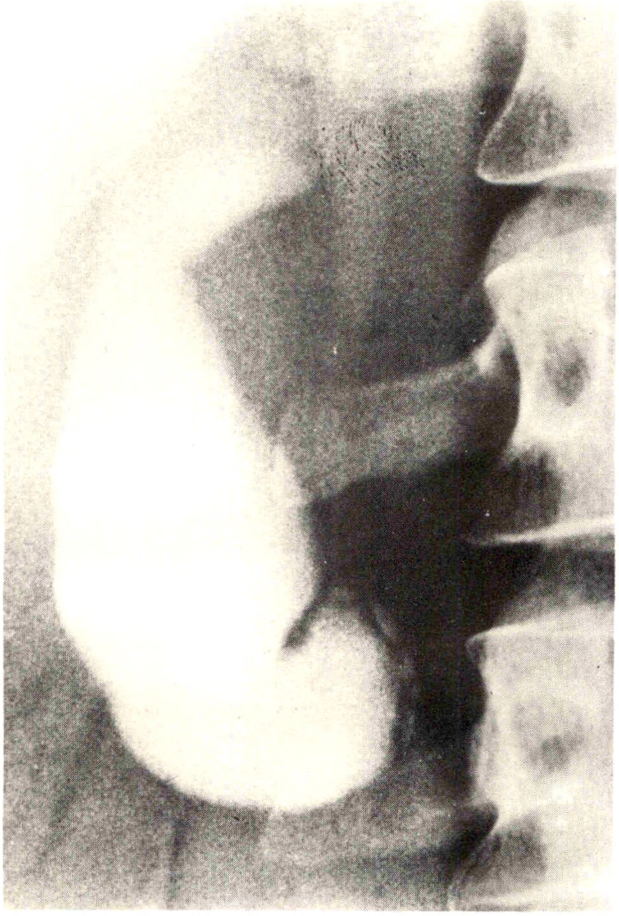

Fig. 1a

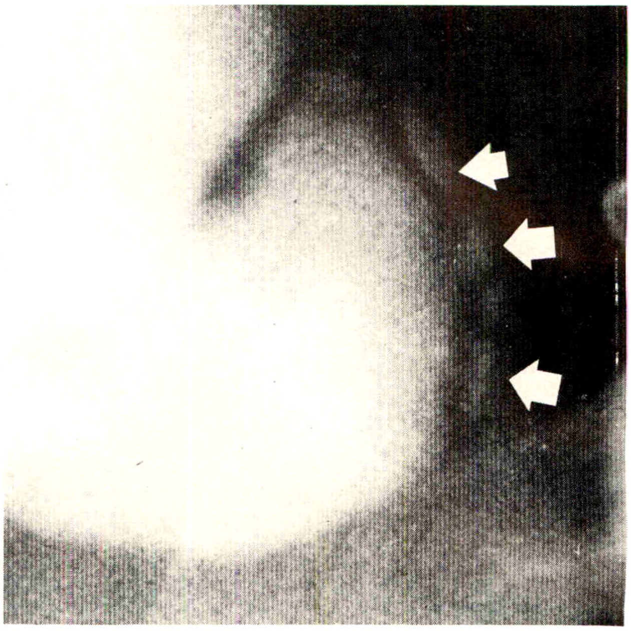

Fig. 1b

Figs. 1a and 1b—Rokitansky-Aschoff sinuses.
a. On this frontal view of the gallbladder, localized adenomyomatosis is demonstrated.
b. (Magnified view) The small oval contrast collections (arrows) represent contrast-filled intramural diverticula or Rokitansky-Aschoff sinuses. The adjacent septation is wider than 2 mm. and thus represents adenomyomatosis which is probably superimposed on a Phrygian cap anomaly.

parallel the lumen of the gallbladder. They are separated from it by a radiolucent line representing the gallbladder wall. The thickness of this line may vary during the examination depending on the degree of gallbladder distention. In addition, one may intermittently see opaque filaments crossing the lucent line which represent the communicating ducts between the intramural sacs and the gallbladder lumen. These are usually filled when the intramural pressure is higher and thus they are more frequently demonstrated after the gallbladder has contracted. Concretions may be present within the intramural diverticula. These stones may prevent the diverticula from filling with contrast material. If sufficiently calcified, the concretions may actually be visualized on plain films as small, rounded densities in the gallbladder region.

The segmental type of adenomyomatosis may be associated with a Phrygian cap anomaly (Figs. 2a and 2b). This is an anomaly characterized by a septation of the gallbladder which is caused by folding of adjacent parts. According to Colquhoun,[4] such a congenital septation should not measure more than 2 mm. in thickness since it usually only represents adjacent epithelial layers separated by small amounts of submucosal tissues. Jutras[1, 2] believes that anything that impedes bile flow from the gallbladder lumen predisposes toward the development of adenomyomatosis. Thus, the Phrygian cap anomaly is a predisposing factor which will favor the development of adenomyomatosis. It is usually segmental in type, involving the fundus of the gallbladder since the Phrygian cap anomaly usually occurs in this location. It should be emphasized, therefore, that any septation greater than 2 mm. in thickness should be suspected of representing adenomyomatosis and other features of the disease should be searched for.

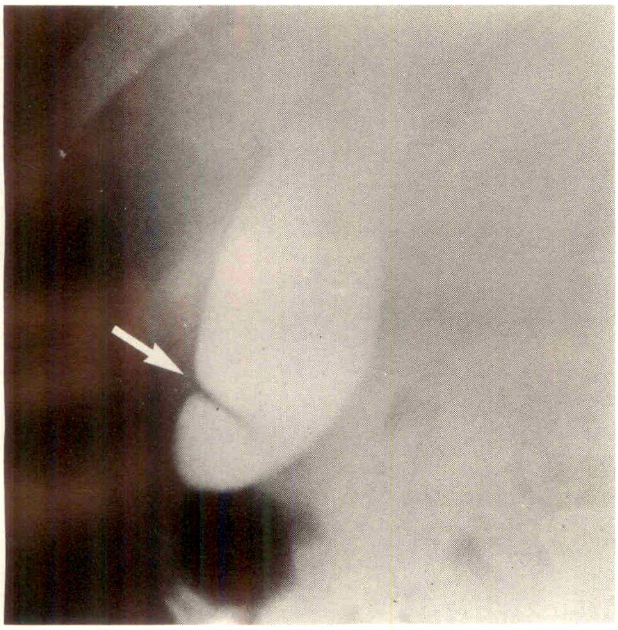

Fig. 2a

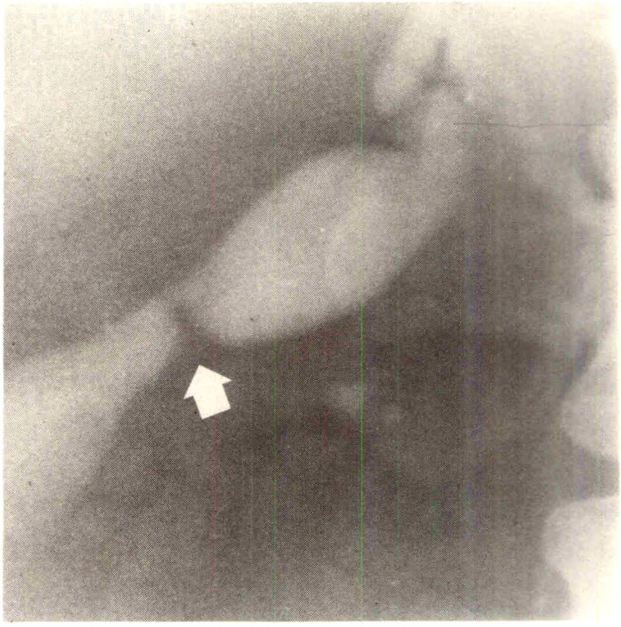

Fig. 2b

Fig. 2a—Phrygian cap anomaly.
On this oblique view from an oral cholecystogram, a Phrygian cap anomaly is demonstrated (arrow). The septum is thin and in a typical location (fundus of gallbladder).

Fig. 2b—Segmental adenomyomatosis.
The gallbladder is concentrically constricted in its mid portion (arrow). This is more clearly demonstrated when compression is applied.

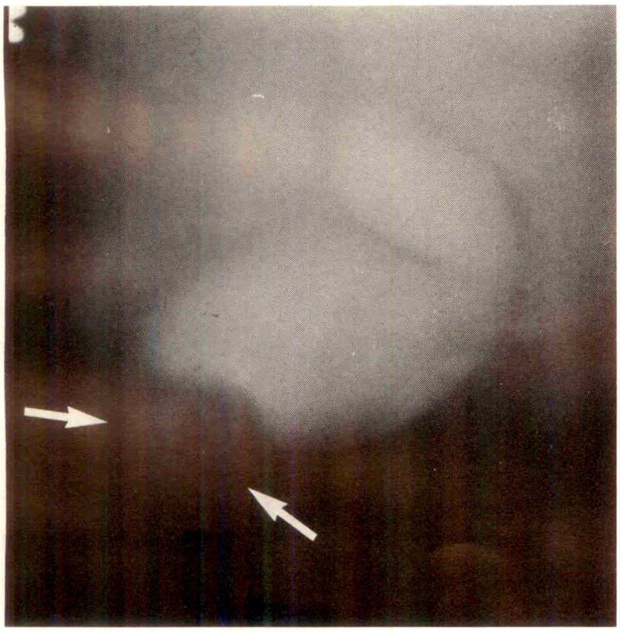

Fig. 3a

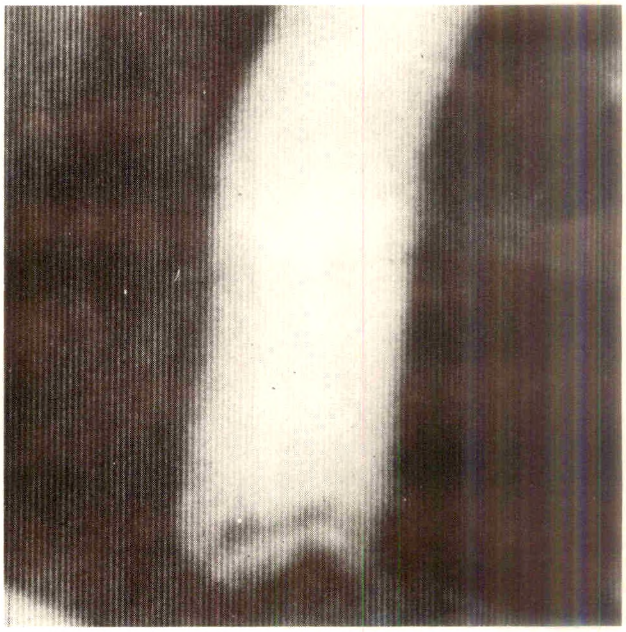

Fig. 3b

Figs. 3a and 3b—Localized adenomyomatosis.
The contrast collection adjacent to the fundus of the gallbladder represents a conglomerate of opacified intramural diverticula (arrows).
The adjacent lumen of the fundus of the gallbladder is impressed, indicating that the adenomyoma is in a transmarginal location.

a. Front view of fundal adenomyoma.
b. Profile view of fundal adenomyoma.

The localized form of adenomyomatosis typically occurs in the fundus of the gallbladder. It may occur, however, occasionally in other parts. On oral cholecystography, the lesion may appear intraluminal, transmarginal or extraluminal (Figs. 3a and 3b). The lesion is diagnosed with a high degree of reliability if it can be demonstrated both *en face* and in profile. It is important to remember that such localized adenomyomatosis or an adenomyoma may change in size and appearance during the examination as the degree of gallbladder distention varies and as compression is applied.

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EDITORIAL

Our New Look

With this issue the American College of Gastroenterology joins the growing number of professional organizations that have increased the size of their journals to 8½ × 11 inches. This change allows us to utilize modern offset printing technics to replace our former letterpress method, thus insuring more rapid production of the Journal. In addition the change is of considerable help to our advertisers, whose materials require the larger format.

Leafing through the pages of this issue, the reader will find a number of other changes that we hope will make the Journal more attractive and readable. The new cover is easier to scan, with the print on a white rather than a yellow background. The inside format has been modified to employ a new and sharp typeface.

More than cosmetic changes are intended for the Journal in 1980. The Editorial Advisory Board will be enlarged to include a sound geographic and professional representation of the expanded membership of the College and the interests of our readers. Much greater use of solicited editorials and the development of a regular section for correspondence are in the planning stage. A mail survey of our readership is planned in order to gauge the relative merits and desirability of our features and articles and to solicit suggestions for new presentations. Revised editorial and printing procedures will allow more efficient distribution of the Journal so that it will reach our readers on time each month.

We of the editorial staff look forward to 1980 as a year of development and growth for the Journal. We welcome the suggestions of our readers.

ARTHUR E. LINDNER, M.D., F.A.C.G.
EDITOR-IN-CHIEF

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NEWS NOTES

AMERICAN COLLEGE OF GASTROENTEROLOGY ELECTS NEW OFFICERS

At the Annual Meeting of the Fellowship of the American College of Gastroenterology held at The Disneyland Hotel in Anaheim, CA, on 22 October 1979, new Officers, Trustees and Governors were elected.

The new President-elect is Burton I. Korelitz, M.D., F.A.C.G., New York, NY: Vice Presidents, Arthur E. Cocco, M.D., F.A.C.G., Baltimore, MD and Walter Harvey Jacobs, M.D., F.A.C.G., Kansas City, MO; Secretary-General, F. Warren Nugent, M.D., F.A.C.G., Boston, MA. David A. Dreiling, M.D., F.A.C.G., New York, NY, was re-elected Treasurer.

Members of the Board of Trustees elected were: S. Philip Bralow, M.D., F.A.C.G., Sarasota, FL; Francis J. Tedesco, M.D., F.A.C.G., Augusta, GA; Franz Goldstein, M.D., F.A.C.G., Philadelphia, PA; Arthur H. Aufses, Jr., M.D., F.A.C.G., New York, NY and Samuel K. Wirtschafter, M.D., F.A.C.G., San Pedro, CA.

Re-elected to the Board of Trustees were: James L. Achord, M.D., F.A.C.G., Jackson, MS; William A. Millhon, M.D., F.A.C.G., Columbus, OH and James L. A. Roth, M.D., F.A.C.G., Philadelphia, PA.

New members of the Board of Governors are: Richard W. McCallum, M.D., F.A.C.G., New Haven, CT; Paul D. Webster, III, M.D., F.A.C.G., Augusta, GA; Phillip M. Berman, M.D., F.A.C.G., Chicago, IL; George B. Rankin, M.D., F.A.C.G., Cleveland, OH; Charles J. Lightdale, M.D., F.A.C.G., New York, NY; Myron Lewis, M.D., F.A.C.G., Memphis, TN and John C. McKechnie, M.D., F.A.C.G., Houston, TX.

Governors re-elected were: Robert L. Berger, M.D., F.A.C.G., Hollywood, FL; Alvin M. Cotlar, M.D., F.A.C.G., New Orleans, LA; Horacio Jinich, M.D., F.A.C.G., Mexico, DF, Mexico; Orlando R. Bordalo, M.D., F.A.C.G., Lisbon, Portugal; Gerardo C. Garrido-Pinson, M.D., F.A.C.G., Lima, Peru; Goro Kakizaki, M.D., F.A.C.G., Miyagi Prefecture, Japan and Augusto Paulino, M.D., F.A.C.G., Rio de Janeiro, Brazil.

Robert L. Berger, M.D., F.A.C.G., Hollywood, FL was re-elected Chairman of the Board of Governors for a third term at the Annual Meeting of the Board of Governors held on Tuesday, 23 October 1979.

Sidney J. Winawer, M.D., F.A.C.G., New York, NY, assumed the Presidency at the meeting.

NEW AUXILIARY OFFICERS

At the Annual Meeting of the Auxiliary of the American College of Gastroenterology held in Anaheim, CA, on Wednesday, 24 October 1979, Mrs. Robert L. Berger, Hollywood, FL, assumed the Presidency.

The new Vice Presidents are: Mrs. L. E. Chapin, Fullerton, CA; Mrs. Robert R. Bartunek, Beachwood, OH; Mrs. J. Edward Berk, Laguna Hills, CA; Secretary, Mrs. Walter H. Jacobs, Shawnee Mission, KS. Mrs. Francis M. Maple, Springfield, MO was re-elected Treasurer and Auxiliary Philanthropic Fund Chairman.

RICHARD H. MARSHAK AWARD

Edward M. Miller, M.D., Albert A. Moss, M.D. San Francisco, CA and Herbert Y. Kressel, M.D., Philadelphia, PA, were given the Annual Richard H. Marshak Award for the best radiology paper published in THE AMERICAN JOURNAL OF GASTROENTEROLOGY in the twelve-month period ended 30 June 1979. Their paper was entitled "Duodenal Involvement with Crohn's Disease: A Spectrum of Radiographic Abnormality" and appeared in the January, 1979 issue of the Journal.

WINNERS OF THE 1979 RORER AWARDS CONTEST

Winners of the awards for the best papers published in THE AMERICAN JOURNAL OF GASTROENTEROLOGY during the twelve months ended on 30 June 1979 were announced at the Annual Convocation of the American College of Gastroenterology in Anaheim, CA, on Sunday, 21 October 1979.

The awards, which are given by the College in cooperation with William H. Rorer, Inc. of Fort Washington, PA, were made to the following:

First Prize of $500.00 was awarded to Joel Panish, M.D., F.A.C.G., of Los Angeles, CA, for his paper entitled "Management of Patients with Polypoid Lesions of the Colon—Current Concepts and Controversies" which was published in the March, 1979 issue.

The Second Prize of $300.00 was awarded to Basil I. Hirschowitz, M.D., F.A.C.G. and Rene G. Gibson, M.D., of Birmingham, AL, for their paper entitled "Effect of Cimetidine on Stimulated Gastric Secretion and Serum Gastrin in the Dog", published in the November, 1978 issue.

The Third Prize of $200.00 went to J. Edward Berk, M.D., F.A.C.G., Louis Fridhandler, Ph.D. and Sidney F. Webb, M.D., all at the Division of Gastroenterology, University of California Irvine Medical Center, Orange, CA. The paper which was published in the June, 1979 issue was entitled "Does Hyperamylasemia in the Drunken Alcoholic Signify Pancreatitis?"

In Memoriam

HENRY BAKER, M.D., F.A.C.G.

It is with a sense of great loss that we record the passing of Henry Baker, M.D., F.A.C.G., Life Fellow, Brookline, MA.

Dr. Baker was a past President of the American College of Gastroenterology, who despite having a great number of other obligations, maintained a keen interest in the College activities. During his many years of affiliation Dr. Baker had served on the Board of Trustees, had been Chairman of the Program Committee and enjoyed attending the annual conventions where he met many of his friends and colleagues.

To evidence his interest in College affairs in a tangible way, Dr. Baker endowed the Annual Lecture given at the convention which bears his name. The first Dr. Henry Baker Lecture was delivered in 1974 and he selected F. Warren Nugent, M.D., F.A.C.G. of Boston, the Chairman of the Department of Gastroenterology of the Lahey Clinic for this honor.

During his lifetime Dr. Baker was honored on many occasions by his professional colleagues and others for his endeavors both in medicine and in community activities. The Intensive Care Unit at the Brookline Hospital, where he served as the Chief of Medicine for many years, was dedicated in his name several years ago. The presence of representatives of the College at the ceremonies gave him great pleasure.

His wise counsel at Board meetings and his presence at our annual conventions will be missed by his friends and acquaintances alike.

We also record with profound sorrow the passing of Abe Alper, M.D., F.A.C.G., Fellow, Hewlett, NY; James T. Brosnan, M.D., F.A.C.G., Fellow, Worcester, MA; Jacques Caroli, M.D., F.A.C.G. (Hon.), Paris, France; Mor J. McCarthy, M.D., Associate Fellow, Kailua, HI; Helmuth Nathan, M.D., F.A.C.G., Fellow, New York, NY; Heinrich Necheles, M.D., F.A.C.G., Fellow, Walnut Creek, CA; Jesse J. Serwer, M.D., Member, Hollywood, FL; Roy Lyman Sexton, M.D., F.A.C.G., Fellow, Silver Spring, MD; Leonard Shapiro, M.D., F.A.C.G., Life Fellow, Palm Beach, FL and Leonard D. Williams, M.D., F.A.C.G., Fellow, Hope, NJ.

We extend our deepest sympathies to the bereaved families.

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THE LAST PAGE*

Questions in Gastroenterology

CHARLES G. HAZZI, B.D., F.A.C.P., F.A.C.G.*
New York, N. Y.

The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the article can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. ALCOHOL FEEDING AND AUTONOMIC NEUROTRANSMITTERS:

A. Experimental alcohol feeding has resulted in atrophy of submaxillary glands but hypertrophy of cardiac ventricles.

B. In both cases there was increase in norepinephrine concentration.

C. There is also an increase in the acetylcholine choline synthesizing enzyme, choline acetylase in the salivary glands, adrenal and pancreas.

D. The above findings do not suggest that chronic alcohol ingestion increases both cholinergic and adrenergic tone.

(Page 21)

2. MEMBRANOUS OBSTRUCTION OF THE INFERIOR VENA CAVA:

A. Is caused by a congenital membrane occurring at the level of the diaphragm.

B. Involves the hepatic veins in most cases.

C. Leads to symptoms of the Budd Chiari syndrome generally before those of I.V.C. obstruction.

D. Is best treated by transcardiac membranotomy.

(Page 28)

3. GASTRIN AND CHRONIC ALCOHOLIC PANCREATITIS:

A. Gastric acid hypersecretion is common in severe pancreatic insufficiency.

B. Experimental pancreatic atrophy in dogs is associated with high serum gastrin.

C. Serum gastrin response to a protein meal or I.V. arginine is exaggerated in patients with chronic pancreatitis and insufficiency.

D. Gastrin response to a protein meal may be absent in some healthy subjects.

(Page 33)

4. DISSEMINATED C.M.V. INFECTION IN THE BOWEL:

A. Less than 25% of adults have antibodies to C.M.V.

B. Gastrointestinal involvement only occurs in the compromised host.

C. Bowel pathology consists of mucosal ulcerations with typical inclusions in epithelial and capillary endothelial cells.

D. In patients taking corticosteroids C.M.V. inclusions are often found in the pre-existing gastrointestinal lesions.

(Page 37)

5. GASTRIC CHORIOCARCINOMA:

A. Probably represents dedifferentiation of adenocarcinoma cells rather than true primary choriocarcinoma.

B. When mixed adeno- and choriocarcinoma are present in the same gastric lesion, the two elements metastasize in the same way.

C. Immunoperoxidase staining may demonstrate human chorionic gonadotropin in cells of both elements when they coexist.

D. H.C.G. has not been demonstrated in typical pure gastric carcinomas.

(Page 45)

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*Associate Professor of Clinical Medicine, New York University School of Medicine.

6. REYE'S SYNDROME:

A. Is probably caused by a common mitochondrial insult compromising energy dependent systems in several tissues.

B. Commonly recurs in survivors, suggesting a genetic predisposition.

C. In addition to diffuse microvesicular fatty change, periportal hepatic necrosis has been seen in some cases.

D. Low initial blood ammonia levels and lack of hepatic glycogen depletion increase the chances of survival.

(Page 49)

7. CHOLESTASIS OF PREGNANCY:

A. Mean onset of icterus is at 26 weeks and is usually preceded by pruritus.

B. Serum bilirubin in most cases is above 10 mg%.

C. There is significant fetal morbidity and fetal bile acid levels are elevated.

D. Increased incidence of gallbladder disease in the mother may be related to alterations in bile acid pools and lipid metabolism when compared to normal pregnant women.

(Page 54)

8. SYPHILITIC HEPATITIS:

A. Is an uncommon complication of early syphilis.

B. Results in disproportionate elevations of the SGOT as compared to the alkaline phosphatase.

C. Has revealed portal inflammation and focal necrosis in all cases biopsied.

D. Is almost always associated with the presence of spirochetes on liver biopsy.

(Page 60)

9. INFLAMMATORY FIBROID POLYP:

A. Most common site is the duodenum.

B. Most common presentation is anemia and bleeding.

C. The lesion appears to arise from the submucosa.

D. Tissue eosinophilia may be striking and commonly associated with peripheral blood eosinophilia.

(Page 62)

10. *STRONGYLOIDES STERCORALIS:*

A. Requires an intermediate life cycle outside the host; autoinfection cannot occur.

B. Clinical manifestations may mimic peptic ulcer and radiographic features may suggest Crohn's disease.

C. Hyperinfection with dissemination of larvae occurs in debilitated or immunosuppressed patients.

D. Diagnosis is usually made by finding eggs in the stools.

(Page 65)

11. FLEXIBLE SIGMOIDOSCOPY:

A. A single phospho-soda enema is an inadequate preparation for this examination.

B. Complications are not more frequent than with a rigid sigmoidoscopy.

C. If a polyp is found on the initial examination, it may be removed safely.

D. The examination is not safe for a patient with acute inflammatory bowel disease.

(Page 70)

12. COLONIC VARICES:

A. Have been associated only with cirrhosis not with splenic or mesenteric vein thrombosis.

B. Are more common in the right side of the colon than in the rectum.

C. Can be reliably detected with barium enema.

D. May require segmental resection of the colon when they cause massive bleeding.

(Page 73)

13. PEPTIC ULCER IN CHILDREN:

A. In infancy, 80% of ulcers are secondary to burns, intracranial lesions, sepsis, shock, etc.

B. Primary ulcers in children are as often gastric as duodenal.

C. Duodenal ulcer in childhood is associated with a 20% positive family history.

D. When surgery is indicated, partial gastrectomy is the treatment of choice.

(Page 75)

14. ADENOMYOMATOSIS OF THE GALLBLADDER:

    A. Histologic changes include invaginations of the mucosa (Rokitansky-Aschoff sinuses).

    B. A hyperfunctioning state may be evident radiologically (hyperconcentration; faster and more complete emptying).

    C. Segmental involvement of the fundus often accompanies a Phrygian cap anomaly.

    D. The localized form (adenomyoma) typically occurs in the fundus.

(Page 81)

Answers to Questions on *The Last Page*

The following are the answers to the questions which appeared on *The Last Page* during the six months, commencing with the July, 1979 issue. The next set of answers for the period from January to June, 1980, will appear in the July, 1980 issue.

July, 1979

1. D
2. B,C,D
3. A
4. C
5. All
6. All
7. A,B,C
8. B,C
9. A,C,D
10. A,C,D
11. A,B
12. C,D
13. B,C
14. A,C
15. D

August, 1979

1. A,B,C,D
2. A,C
3. A,B
4. A,B
5. D
6. A,B,D
7. B,C
8. C,D
9. A,D
10. B,C,D
11. A,B,C
12. A,B,D
13. B

September, 1979

1. A,B,C
2. B
3. All
4. All
5. A,C,D
6. B,C
7. D
8. A,D
9. A,C,D
10. A,C
11. A,B,D
12. A,B
13. A,B,D
14. All

October, 1979

1. A,B,D
2. C
3. C,D
4. B,C
5. A,B
6. C,D
7. A,B
8. A,B
9. A,B
10. A
11. B,D
12. A,C,D
13. A,B,D

November, 1979

1. A
2. A,B
3. A,C
4. D
5. A,B
6. A,B
7. B,D
8. B,D
9. B,C
10. A,B,C

December, 1979

1. A,B
2. A,B
3. B,C,D
4. D
5. A,C
6. B,C
7. B,D
8. A,B,C
9. A,B,C
10. D
11. B,D
12. A,C,D

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Papers to be presented before the 45th Annual Convention of the American College of Gastroenterology.

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Cortenema®
disposable unit-dose
hydrocortisone retention enema

COMPOSITION: Each 60 ml. unit contains Hydrocortisone, 100 mg. in an aqueous solution of carboxypolymethylene, polysorbate 80, and methylparaben, 0.18% as a preservative.
INDICATIONS: Adjunctive therapy in ulcerative colitis, especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
CONTRAINDICATIONS: Systemic fungal infections; recent ileocolostomy.
WARNINGS: In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.

Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
ADVERSE REACTIONS: Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
HOW SUPPLIED: Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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CORTENEMA®

(disposable unit-dose hydrocortisone retention enema)

First choice in treating distal ulcerative colitis is Cortenema. It provides fast, topical relief of discomfort due to bleeding, diarrhea and tenesmus within days. An immediate course of Cortenema usually brings about remission of the sigmoidoscopic signs within three weeks. This usual course costs far less than even a single day of hospitalization. Difficult cases may require longer term therapy. Cortenema may be represcribed as needed during subsequent exacerbations. Cortenema: convenient, topical steroid therapy, seldom accompanied by systemic effects. First choice in treating distal ulcerative colitis.

See preceding page
for a brief summary
of prescribing information.

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MEETINGS OF INTEREST

45th Annual Convention, American College of Gastroenterology, Hilton Harbour Castle, Toronto, Canada, 13-15 October 1980.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Hilton Harbour Castle, Toronto, Canada, 16-18 October 1980.

Ninth Annual William Beaumont Gastrointestinal Symposium, William Beaumont Army Medical Center, El Paso, TX, 19-21 March 1980.

Liver Disease Update 1980, Co-sponsored by the American College of Gastroenterology, the University of Mississippi School of Medicine Division of Digestive Diseases and the University Medical Center Division of Continuing Health Professional Education, Holiday Inn Downtown, Jackson, MS, 10, 11, 12 April 1980.

Course on Inflammatory Bowel Disease: Experience and Controversy, Co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 11, 12, April 1980.

Practical Gastroenterology for the Primary Care Physician, UCLA extension, The Miramar-Sheraton, Santa Monica, CA, 16, 17 February 1980.

The Colon and Its Diseases, American Gastroenterological Association, Salt Palace, Salt Lake City, UT, 17, 18 May 1980.

Endoscopy Update—1980, American Society for Gastrointestinal Endoscopy, Salt Lake City, UT, 22, 23 May 1980.

AZULFIDINE®
(sulfasalazine, N.F.)
Tablets and EN-tabs®

INDICATIONS: AZULFIDINE (sulfasalazine, N.F.) is indicated in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. AZULFIDINE EN-tabs are particularly indicated in patients who experience gastrointestinal intolerance after the first few doses of the drug, when such intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites and in those for whom a reduction in dosage does not alleviate the gastrointestinal effects.

CONTRAINDICATIONS: Hypersensitivity to sulfonamides or salicylates. In infants under 2 years. Intestinal and urinary obstruction. Pregnancy at term and during the nursing period. In patients with porphyria.

WARNINGS: The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.

Deaths associated with the administration of AZULFIDINE (sulfasalazine, N.F.) have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and CNS changes and fibrosing alveolitis.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders.

Complete blood counts as well as urinalysis with microscopic examination should be done frequently.

PRECAUTIONS: Administer with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia.

Maintain adequate fluid intake to prevent crystalluria and stone formation.

ADVERSE REACTIONS: Adverse reactions have been observed in 5 to 55% of patients included in clinical studies reported in the literature. Experience suggests that with daily dosages of 4 g or more, adverse reactions tend to increase. The most common adverse reactions associated with AZULFIDINE therapy are anorexia, nausea, vomiting, and gastric distress. The following adverse reactions have been reported to occur during therapy with AZULFIDINE.

Blood dyscrasias: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, Heinz Body anemia, purpura, hypoprothrombinemia, "cyanosis," and methemoglobinemia.

Hypersensitivity reactions: Generalized skin eruptions, erythema multiforme (Stevens-Johnson syndrome), parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, pruritus, urticaria, photosensitization, anaphylaxis, serum sickness syndrome, chills, drug fever, periorbital edema, conjunctival and scleral injection, arthralgia, transient pulmonary changes with eosinophilia and decreased pulmonary function, allergic myocarditis, polyarteritis nodosa, L.E. phenomenon, and hepatitis with immune complexes.

Gastrointestinal reactions: Anorexia, nausea, emesis, abdominal pains, diarrhea, bloody diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.

CNS reactions: Headache, vertigo, tinnitus, hearing loss, peripheral neuropathy, transient lesions of posterior spinal column, transverse myelitis, ataxia, convulsions, insomnia, mental depression, hallucinations and drowsiness.

Renal reactions: Crystalluria, hematuria, proteinuria, and nephrotic syndrome. Toxic nephrosis with oliguria and anuria.

Incidents of alopecia and reduction in sperm count and viability have also been reported.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross sensitivity may exist with these agents.

AZULFIDINE (sulfasalazine, N.F.) produces an orange-yellow color when the urine is alkaline. Similar discoloration of the skin has also been reported.

SUPPLIED: Tablets and EN-tabs (enteric-coated) 0.5 gm. in bottles of 100 and 500. Also available as Azulfidine Unit Dose in boxes of 100's and 1000's.

IMPORTANT: See full prescribing information before administering AZULFIDINE.

References:
1. Dissanayake, A.S. and Truelove, S.C.: *Gut 14*:923-926, 1973.
2. Azad Kahn, A.K., Howes, D.T., Piris, J. and Truelove, S.C.: *Gut 18*:421-422, 1977.

Pharmacia

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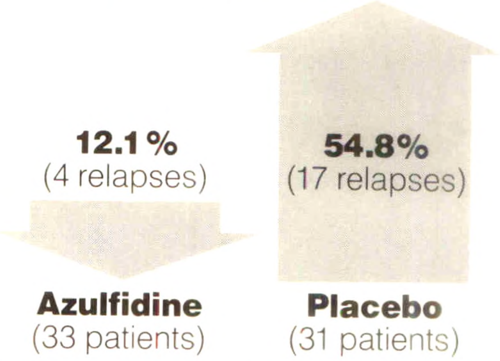
Help your patient avoid the ups & downs of ulcerative colitis.

Gain control with Azulfidine® (sulfasalazine, N.F.).

- Drug of choice in ulcerative colitis therapy for over 30 years
- Unmatched record of clinical efficacy
- Reliable management for a major chronic disorder

Maintain control and help prevent flare-ups.

4½ times fewer relapses with Azulfidine[1]
Relapse rate after six months:



Such data provide "a good case for continuing maintenance treatment with sulphasalazine [Azulfidine] indefinitely provided there are no harmful side effects."[1]

Further clinical study confirms optimal daily dose[2]
"...a daily dose of 2 g is suitable for general use as long-term maintenance treatment."[2]

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(sulfasalazine, N.F.)

A proven track record in ulcerative colitis therapy for over 30 years.

Pharmacia

See facing page for brief summary of prescribing information.
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Colonoscopy Congress

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CLINICAL GASTROENTEROLOGY UPDATE
ANNUAL POSTGRADUATE COURSE
of the
AMERICAN COLLEGE OF GASTROENTEROLOGY
16, 17, 18 October 1980
Toronto Hilton Harbour Castle
Toronto, Canada

New and comprehensive material facilitating the diagnosis and treatment of acute and chronic liver disease, portal hypertension, upper and lower gastrointestinal bleeding, gastrointestinal cancer, inflammatory bowel disease and enteral and parenteral nutrition will be presented by a distinguished faculty including: Drs. S. Sherlock, Maddrey, E. Schiff, Silverstein, Athanasoulis, Farmer, Nugent, Waye, Tedesco, Korelitz, P. Sherlock, Veidenheimer, Jeejeebhoy and Winawer.

The course is clinically oriented and is aimed at those who are engaged in the management of patients with digestive diseases.

The Director for the course is Harold Bernhard, M.D., F.A.C.G.

Further information and registration forms may be obtained from:
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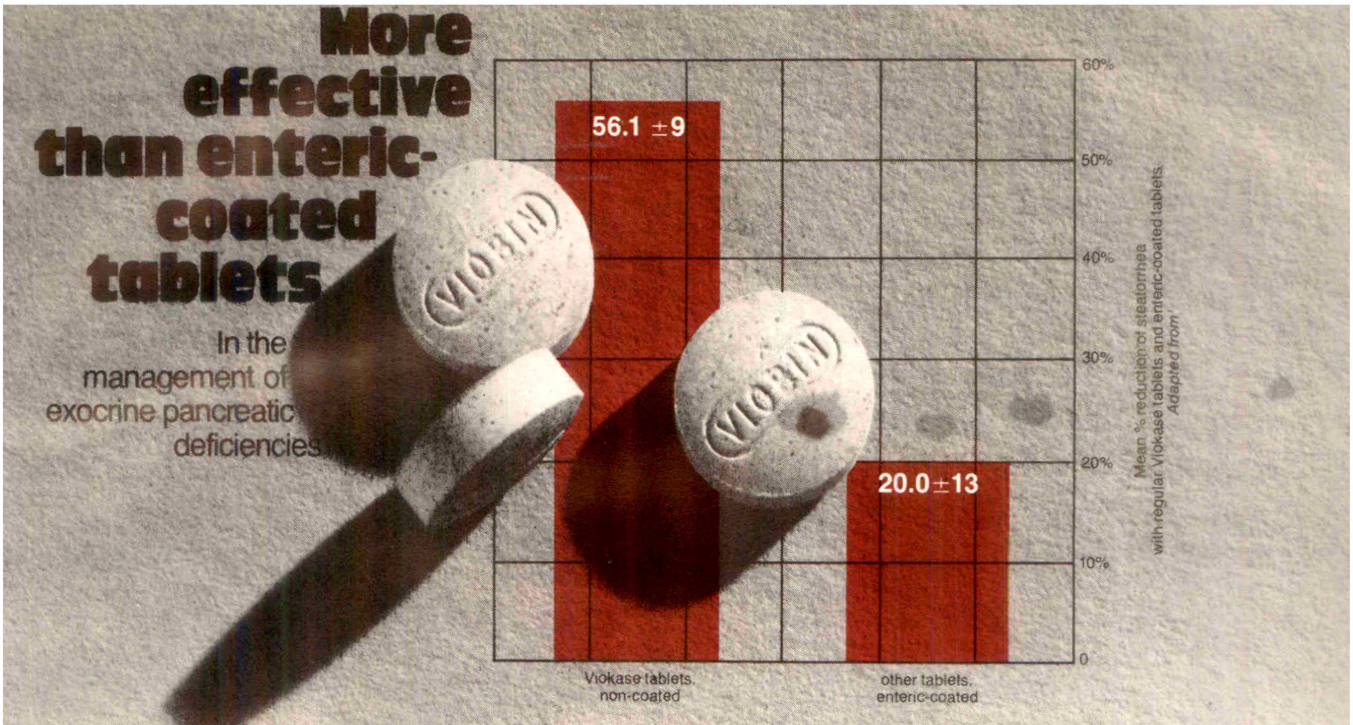
More effective than enteric-coated tablets

In the management of exocrine pancreatic deficiencies



VIOKASE®

Each 325 mg. Tablet contains: Lipase, N.F. Units 6,500; Protease, N.F. Units 32,000; Amylase, N.F. Units 48,000

In a recent study, regular pancreatic enzyme tablets, such as Viokase, were found to be nearly three times as effective as enteric-coated tablets in correcting steatorrhea.[1] Theoretically, the enteric coating protects the enzymes from the stomach's acidity and releases them in the alkaline environment of the small intestine. But in patients with pancreatic insufficiency, the duodenum and upper jejunum are often acidic.[2] As a result, enteric coatings "...may reduce the clinical effectiveness of the pancreatic extracts".[1]

Another study reports that, "In the dosages used, neither enteric-coated enzymes nor supplemental neutralizing antacids were more effective than pancreatin alone in decreasing steatorrhea or improving duodenal enzyme delivery."[3] The authors tentatively conclude that "...acid-resistant enteric-coated preparations are helpful only in selected cases in which postprandial intragastric pH is uniformly low".[3] Thus, enteric-coated preparations appear to have limited usefulness in the treatment of exocrine pancreatic insufficiency, and when they are used, their effectiveness should be tested by determination of the response of steatorrhea.[1]

Viokase still costs less

Based on figures published in the 1979 *Drug Topic Redbook,* daily therapy with Viokase can cost your patients less than half the price of enteric-coated products...and the effectiveness of Viokase is confirmed by over 25 years of clinical experience.

VIOKASE® (pancreatin)

Description: VIOKASE is a pancreatic enzyme concentrate of porcine origin containing standardized amylase, protease and lipase activities plus esterases, peptidases, nucleases and elastase.

The enzyme potency of the tablets and powder are:

	Each 325 mg. Tablet	Each 0.75 gram (⅓ teaspoonful)
Lipase, N.F. Units	6,500	15,000
Protease, N.F. Units	32,000	75,000
Amylase, N.F. Units	48,000	112,500

Under conditions of the N.F. test method (in vitro) VIOKASE has the following total digestive capacity:

	Each 325 mg. Tablet	Each 0.75 g. Powder
Dietary Fat	23	53 grams
Dietary Protein	32	75 grams
Dietary Starch	48	112 grams

VIOKASE Tablets are not enteric coated.

Indications: As a digestive aid in cystic fibrosis and in exocrine pancreatic deficiencies usually due to chronic pancreatitis, pancreatectomy or obstruction in the pancreas caused by malignant growth.

Administration and Dosage:

Powder: Dosage to patients with cystic fibrosis: ⅓ teaspoon (0.75 grams) with meals.

Tablets: Dosage to patients with cystic fibrosis or chronic pancreatitis —1 to 3 tablets with meals. For aiding digestion in patients with pancreatectomy or gastrectomy—1 to 2 tablets taken at 2-hour intervals, or as directed by physician.

Caution: Federal law prohibits dispensing without prescription.

Warnings: Avoid inhalation of powder.

Precautions: Use with caution in patients known to be allergic to pork protein.

How Supplied:

Powder: Bottles of 4 ounces and 8 ounces

Tablets: Bottles of 100 and 500

Literature Available: Complete literature available upon request including information on BEEF VIOKASE DERIVED FROM BEEF PANCREAS FOR THOSE EXCEPTIONAL PATIENTS ALLERGIC TO PORK.

1. Graham, David Y., M.D.: Enzyme Replacement Therapy of Exocrine Pancreatic Insufficiency in Man: N. Engl J. Med *296*: 1314-1317, 1977.

2. Benn, A. and Cooke, W.T.: Intraluminar pH of Duodenum and Jejunum in Fasting Subjects with Normal and Abnormal Gastric or Pancreatic Function. Scand J. Gastroenterol *6*: 313-317, 1971.

3. Regan, Patrick T., M.D., Malagelada, Juan-R. M.D., DiMagno, Eugene P., M.D., Glanzman, Scotty L. and Go, Vay Liang W., M.D.: Comparative Effects of Antacids, Cimetidine and Enteric Coating on the Therapeutic Response to Oral Enzymes in Severe Pancreatic Insufficiency; N. Engl J. Med *297*: 854-858, 1977.

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HEPATIC-AID™
(SUSPENDABLE POWDER)

Hepatic encephalopathy is a very real threat to patients suffering from chronic liver disease, and is often precipitated or exacerbated by dietary protein. Such protein-intolerant patients may require a special dietary supplement high in branched chain amino acids and low in aromatic amino acids.* These patients will benefit from Hepatic-Aid.

Hepatic-Aid is an enteral nutritional supplement that supplies calories and a pattern of amino acids specifically formulated to meet the nutritional needs of patients with impaired liver function. It is high in the branched chain amino acids valine, leucine, and isoleucine; high in arginine (an ammonia-processing amino acid); low in the aromatic amino acids phenylalanine, tyrosine, and tryptophan, and low in methionine. Results from clinical studies have demonstrated a positive nitrogen balance in stable protein-intolerant patients with chronic liver disease. In those studies Hepatic-Aid supplied 40 to 60 grams of amino acids and adequate calories as a supplement to a 20 gram conventional protein diet.

Hepatic-Aid also tastes good. Extensive flavor-formulation research and testing has resulted in three appealing flavors: artificial chocolate, custard and eggnog. Since patients are more likely to follow an oral diet they enjoy, the result could be a more favorable outcome to their clinical condition.

Hepatic-Aid: the first dietary supplement that is ideal for the nutritional repletion of patients with impaired liver function. You can rely on its quality because it's from McGaw—The Total Clinical Nutrition Company.

If you have a question about the use or formulation of any McGaw product and need an answer immediately, call the McGaw STAT-LINE™ any time, day or night, toll free: 800-854-6851. In California, Hawaii, and Alaska, call collect: 714-754-2147.

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*Comparison made to amino acid patterns of proteins of high biological value.